UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF LOUISIANA

LOUISIANA HEALTH SERVICE AND INDEMNITY COMPANY d/b/a BLUE CROSS BLUE SHIELD OF LOUISIANA and HMO LOUISIANA, INC. on behalf of itself and all others similarly situated, *Plaintiffs ,* vs. ALLERGAN, INC., *Defendant.*	Civil Action No. 3:18-cv-186 SDD-RLB

COMPLAINT AND JURY TRIAL DEMAND

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I. INTRODUCTION

1. This action arises from Allergan, Inc.'s ("Allergan") scheme to unlawfully prolong its monopoly over the sale of cyclosporine ophthalmic emulsion, 0.05% in the United States. It seeks damages on behalf of Louisiana Health Services and Indemnity Company d/b/a Blue Cross Blue Shield of Louisiana (hereafter, BCBSLA) and HMO Louisiana, Inc. (Plaintiffs), by and through the undersigned counsel, on behalf of themselves and a class of similarly situated individuals and entities (the "Class"), that bought Restasis® (generic name, cyclosporine ophthalmic emulsion, 0.05%) directly from Allergan from May 2014 to the present.

2. Allergan violated sections 1 and 2 of the Sherman Act, 15 U.S.C. §§ 1 & 2, through a scheme to monopolize involving a series of unlawful acts.

3. *Fraud on the PTO.* Although it had legitimate patent coverage for Restasis through May 2014, Allergan obtained follow-on patents for Restasis by defrauding the United States Patent and Trademark Office ("PTO"), therein extending Restasis's ostensible term of patent coverage for many more years. Allergan represented to the PTO that clinical trials testing a lower strength Restasis formulation showed unexpected effectiveness and surprising results. But these clinical representations were false. Allergan derived these representations by cherry-picking favorable test results, ignoring the vast majority of results that did not support its claims and concealing them from the PTO. Allergan also failed to tell the PTO that data it relied on lacked statistical significance. What's more, Allergan misled the PTO to believe this data was newly discovered, when in fact it had been published a decade earlier and was prior art to the second wave Restasis patents. Not knowing the truth about Allergan's "data," the PTO relied on Allergan's misrepresentations and issued the second wave patents.

4. *Wrongful Orange Book listings.* Allergan listed the second wave patents in the FDA's Orange Book knowing that those patents did not fall under the listing requirements and

should not be asserted against potential generic competitors: Those patents had been procured by fraud, and Allergan knew it. As a result, Allergan knew it had no entitlement to the protections the Orange Book affords patent holders. The listings were also wrongful because no reasonable company in the position of Allergan could have realistically expected to prevailing on the merits of litigation enforcing those second wave patents: the invalidation of the second wave patents was inevitable because the data Allergan relied on to obtain the patents was prior art to the applications as well as seriously misrepresented.

5. *Wrongful FDA petitions*. Allergan filed baseless petitions with the FDA seeking to have the FDA impose over a dozen unnecessary, time-consuming, and unsupported requirements upon would-be generic competitors seeking to gain approval for generic Restasis products. The petitions, along with numerous supplements, diverted substantial resources of the FDA to answering Allergan's demands. Eventually the FDA, in emphatic language, denied every substantive Allergan demand.

6. *Wrongful patent enforcement*. Using the listed, second wave patents, Allergan filed and pursued at least five infringement actions against would-be makers of generic Restasis. Allergan knew no reasonable litigant could have a realistic expectation of prevailing on the ultimate merits of those cases. But Allergan's purpose in filing and pursuing the suits was not to achieve ultimate patent victories; it was to frustrate the FDA's review of pending applications for generic cyclosporine ophthalmic emulsion, 0.05% and to delay the ability of would-be generics to enter that market.

7. *Conspiracy to monopolize and contract in restraint of trade*. After the PTO in December 2016 ruled that the second wave patents were likely to be declared invalid during an *inter partes* review, Allergan purported to transfer ownership of the second wave patents to the

Saint Regis Mohawk Tribe ("Mohawk"). Allergan's goal was to use Mohawk's cloak of sovereign immunity to defeat the PTO's jurisdiction over the patents, nullifying the PTO's ability to invalidate them. The Allergan-Mohawk agreement was undertaken to restrain competition unreasonably.

8. Allergan's anticompetitive scheme had its intended consequence of delaying generic competition in the market for cyclosporine ophthalmic emulsion, 0.05%. Were it not for Allergan's unlawful scheme, generic competition for cyclosporine ophthalmic emulsion, 0.05% would have begun as early as May 2014, and direct purchasers would have had access to far less expensive, generic versions of Restasis. Given that Restasis's annual sales often exceed $1 billion, the proposed direct purchaser class was likely overcharged by many hundreds of millions of dollars as a result of Allergan's anticompetitive scheme.

II. PARTIES

9. Plaintiff BCBSLA is a domestic health insurance corporation licensed to conduct business in the State of Louisiana and is involved in the business of providing health benefits, third party administrative services and managing health care services for its insureds and members. BCBSLA has paid and provided, and will in the future pay and provide, health care benefits to its members and insured as a direct result of the wrongful conduct of the Defendants as fully alleged herein.

10. Plaintiff HMO Louisiana, Inc. is a domestic health insurance corporation licensed to conduct business in the State of Louisiana and is involved in the business of providing health benefits, third party administrative services and managing health care services for its insureds and members. Louisiana HMO, Inc. has paid and provided, and will in the future pay and provide, health care benefits to its members and insured as a direct result of the wrongful conduct of the Defendants as fully alleged herein.

11. The defendant, Allergan, Inc., is a Delaware corporation with its principal place of business located in Irvine, California. Allergan is the holder of approved New Drug Application No. 50-790 for cyclosporine ophthalmic emulsion, 0.05%, sold under the Restasis trademark. Allergan was also the applicant for, and holder of, the six second wave patents which it claims cover Restasis: U.S. Patent No. 8,629,111 (issued January 14, 2014); U.S. Patent No. 8,633,162 (issued January 21, 2014); U.S. Patent No. 8,642,556 (issued February 4, 2014), U.S. Patent No. 8,648,048 (issued February 11, 2014), U.S. Patent No. 8,685,930 (issued April 1, 2014), and US 9,248,191 (issued February 2, 2016). As of September 8, 2017, Allergan purports to have transferred its ownership interests in the second wave patents to Mohawk.

12. All of the actions described in this complaint are part of, and in furtherance of, the unlawful conduct alleged herein, and were authorized, ordered, or undertaken by Allergan's officers, agents, employees, or other representatives while actively engaged in the management of Allergan's affairs and within the course and scope of their duties and employment, or with Allergan's actual, apparent, or ostensible authority.

III. JURISDICTION AND VENUE

13. The Court has subject matter jurisdiction under 28 U.S.C. §§ 1331, 1337(a), and 15 U.S.C. § 15. This action alleges violations of sections 1 and 2 of the Sherman Act, 15 U.S.C. §§ 1 & 2. Those violations are actionable under sections 4 and 16 of the Clayton Act, 15 U.S.C. §§ 15(a) & 26. The complaint seeks an injunction and to recover treble damages, interest, and costs of suit and attorneys' fees due to Allergan's unlawful foreclosure of generic competition in the market for cyclosporine ophthalmic emulsion, 0.05% in the United States.

14. Venue is proper in this District pursuant to 15 U.S.C. §§ 15(a) & 22 and 28 U.S.C. § 1391(b), (c), and (d). During the class period (May 2014 to the present), Allergan transacted business, was found, or had agents in this District.

15. This Court has personal jurisdiction over Allergan. Allergan's wrongful conduct had a substantial effect on interstate commerce of the United States, including in this District. During the class period, Allergan manufactured, sold, and shipped Restasis in a continuous and uninterrupted flow of interstate commerce, which included sales of Restasis in this District, advertisement of Restasis in media in this District, monitoring prescriptions of Restasis by prescribers within this District, and employment of product detailers in this District, who as agents of Allergan marketed Restasis to prescribers in this District. Allergan's conduct had a direct, substantial, and reasonably foreseeable effect on interstate commerce, including commerce within this District.

16. Throughout the United States and including in this District, Allergan transacted business, maintained substantial contacts, or committed overt acts in furtherance of the illegal scheme. The scheme has been directed at, and has had the intended effect of, causing injury to persons residing in, located in, or doing business throughout the United States, including in this District.

IV. REGULATORY BACKGROUND

A. New Drug Applications and Orange Book Listings

17. Under the Food, Drug, and Cosmetics Act ("FDCA"), drug companies who wish to sell a new drug product must file a New Drug Application ("NDA") with the FDA. An NDA submission must include specific data concerning the safety and effectiveness of the drug.

18. Under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. Law No. 98- 417, 98 Stat. 1585 (1984) (the "Hatch-Waxman Amendments"), an NDA applicant must submit to the FDA information for each patent that claims the drug or method of using the

drug that is the subject of the NDA (the listed drug) and for which "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[1] The FDA then publishes this information in digest titled *Approved Drug Products with Therapeutic Equivalence Ratings* but known as the Orange Book. The statute further provides that if a drug patent is issued after NDA approval, the NDA sponsor must file that new patent information with FDA not later than 30 days after the date the patent is issued.[2]

19. The FDA performs only a ministerial act in listing the patents brand manufacturers identify in the Orange Book. The FDA does not have the resources or authority to verify the manufacturer's representations for accuracy or trustworthiness. Thus, the FDA relies completely on the manufacturer's truthfulness about the Orange Book information it supplies, including whether the listed patent is valid and may reasonably be asserted against a generic applicant.

20. Once a brand manufacturer lists a patent in the Orange Book, that listing puts potential generic competitors on notice that the brand considers the patent to cover its drug. And the listing triggers important regulatory consequences.

B. Abbreviated New Drug Applications and Hatch-Waxman

21. Congress passed the Hatch-Waxman Amendments to balance the need to provide brand companies with incentives to develop new medicines against the countervailing need to speed the entry of cheaper, equally effective versions of these medications.

[1] 21 U.S.C. § 355(b)(1) & (c)(2).

[2] *Id.* § (c)(2).

22. Designed ensure to the timely introduction of generic drugs onto market, the Amendments enable generic manufacturers to file Abbreviated New Drug Applications ("ANDA") with the FDA for drugs they seek to bring to market. Rather than requiring generic manufacturers to conduct expensive clinical trials to re-prove the drugs' safety and efficacy, the Hatch-Waxman Amendments allow generic manufacturers to rely on the data the brands have already submit to prove the drugs' safety and efficacy. All the generic manufacturer show is that their generic copies are pharmaceutically and bio-equivalent (together, "therapeutically equivalent") to the brands. The premise – codified by Congress and implemented by the FDA for the past thirty years – is that two drug products that contain the same active pharmaceutical ingredient, in the same dose, and delivered in the same way are equally safe and effective.

23. The Amendments also provided a vehicle through which a generic manufacturer can address the drug product and method-of-use patents that cover the drug it seeks to manufacture. An ANDA applicant must include in its application one of the following four certifications with respect to the patents covering the branded drug it seeks to produce:

(I) that such patent information has not been filed (a paragraph I certification);

(II) that such patent has expired (a paragraph II certification);

(III) of the date on which such patent will expire (a paragraph III certification); or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[3]

[3] 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV); *see also* 21 C.F.R. 314.94(a)(12)(i)(A). The FDCA provides only one circumstance in which an applicant with a pending ANDA need not certify to a listed patent, but that exception, relating to method-of-use patents, is not applicable here. 21 U.S.C. § 355(j)(2)(A)(viii); *see also* 21 C.F.R. 314.94(a)(12)(iv).

24. After an ANDA applicant submits its application along with its certification, the FDA decides whether to accept the application. Once an application containing a paragraph IV certification receives acknowledgment from the FDA that the agency has determined the application is sufficiently complete to permit substantive review, the applicant must provide the NDA holder and the patent owner notice of its paragraph IV certification. This notice must include a description of the legal and factual basis for the ANDA holder's assertion that the patent is invalid or not infringed.[4] The statute prohibits an applicant from providing such notice prior to FDA's formal receipt of the application for substantive review.[5]

25. If an NDA holder or patent owner initiates a patent infringement action against an ANDA applicant within 45 days of receiving that applicant's paragraph IV notice, approval of the applicant's ANDA will generally be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order.[6] If a patent is listed in the Orange Book after an ANDA is submitted but before it is approved, the applicant for the pending ANDA generally must amend its application and provide an appropriate certification for the newly listed patent and the attendant notice. Nonetheless, a patent listed after the date an ANDA was accepted for

[4] 21 U.S.C. § 355(j)(2)(B).

[5] *Id.* § 355(j)(2)(B)(ii).

[6] *Id.* § 355(j)(5)(B)(iii). The brand manufacturer could file patent infringement claims more than 45 days after receiving the paragraph IV certification, but doing so would not trigger the automatic 30-month stay of FDA approval.

By enabling the brand maker to bring suit in response to a paragraph IV certification, the Hatch-Waxman Amendments created a procedural mechanism to resolve patent disputes between brand and generic manufacturers before generic products launched to prevent delay of generic entry that such suits would otherwise cause.

filing (i.e., the date the FDA determines it was substantially complete) will not trigger a 30-month stay for that application.[7]

26. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003[8] ("MMA") revised these exclusivity provisions in 2003. These revisions, like the original Hatch-Waxman Amendments, provide the "first applicant(s)" to submit a substantially complete application that contains a paragraph IV certification challenging a patent – and thus the first applicant(s) to undertake the risk of litigation – an incentive in the form of the opportunity to be the *only* generic drug manufacturer on the market with the brand for a 180-day period. Under these provisions, subsequently submitted ANDAs for the same product that contain paragraph IV certifications cannot be approved until after the 180-day exclusivity period has run, unless the first applicant has forfeited this period.[9]

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[7] *Id.* § 355(j)(5)(B)(iii). The applicable text reads that, if there is a paragraph IV certification:

> the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice . . . is received, an action is brought for infringement of the patent . . . before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice . . . or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action . . . . "

The statute provides exceptions to the 30-month stay, including various litigation or settlement scenarios that occur before the 30-month period expires. *Id.*

[8] Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003)

[9] The requirements for obtaining and retaining this 180-day exclusivity period are described at 21 U.S.C. §§ 355(j)(5)(B)(iv) & (j)(5)(D).

Hatch-Waxman thus creates incentives for generics to challenge questionable patents by awarding 180 days of exclusivity to the first paragraph IV-certified ANDA filer. Because the first generic manufacturer to file an ANDA containing a paragraph IV certification receives 180 days of market exclusivity, later ANDA-filers are not permitted to launch their own generic products for at least six months after the first generic – known as the "first filer" – launches its product (or waives or forfeits its exclusivity).

27. The FDCA defines "first applicant" as "an applicant that, on the first day on which a substantially complete application containing a [paragraph IV certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [paragraph IV certification] for the drug."[10]

28. There are six different ways a first applicant can forfeit his or her 180-day period of exclusivity. The last, regarding patent expiration, provides that a forfeiture event occurs if "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired." Notably, "[i]f all first applicants forfeit the 180-day exclusivity period under [21 U.S.C. § 355(j)(5)(D)(ii)] . . . no applicant shall be eligible for a 180-day exclusivity period."[11]

C. The FDA's Determination of Bioequivalence for ANDAs.

29. *ANDA approvals*. The Hatch-Waxman Amendments created Section 505(j)[12] of the FDCA: the ANDA approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and efficacy of its proposed generic drug product. Instead, the applicant relies on the FDA's previous finding that the brand drug (known in this setting as the "reference listed drug") is safe and effective. All the ANDA applicant must show is bioequivalence, *i.e.*, that the drug product described in the ANDA contains the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the reference listed drug.[13]

30. *Regulations provide exacting requirements for ophthalmic ANDAs.* The FDA will

[10] *Id.* § 355(j)(5)(B)(iv)(II)(bb).

[11] *Id.* § 355(j)(5)(D)(iii).

[12] *Id.* § 355(j).

[13] *Id.* §§ 355(u)(2)(A), (u)(2), & (u)(4); *see also* 21 C.F.R. 314.94(a).

refuse to approve an ANDA if it determines that "the inactive ingredients of the drug are unsafe for use" as labeled, or if "the composition of the drug is unsafe for use . . . because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included."[14] The FDA considers the inactive ingredients or composition of a proposed generic drug product unsafe "if, on the basis of information available to the [A]gency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy."[15]

31. In general, the inactive ingredients in a generic topical product need not match those in the reference listed drug so long as the applicant "identifies and characterizes [any] differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."[16] However, generic versions of drugs intended for ophthalmic use (use in the eye), like Restasis, face stricter requirements. Specifically, generic ophthalmic drug products must "contain the same inactive ingredients and in the same concentration as the reference listed drug."[17] However, the applicant's product can differ from the reference listed drug in its "preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."[18] The FDA considers an inactive ingredient in a proposed generic version of an ophthalmic drug "unsafe" unless it is the same concentration (other than allowable

[14] 21 U.S.C. § 355(u)(4)(H); *see also* 21 C.F.R. 314.127(a)(8)(i).

[15] 21 C.F.R § 314.127(a)(8)(ii)(A).

[16] *Id.* § 314.94(a)(9)(v).

[17] *Id.* § 314.94(a)(9)(iv).

[18] *Id.*

differences) as the reference listed drug. The FDA also considers the generic unsafe if the applicant fails to demonstrate that any allowable difference does not affect the safety or efficacy of the proposed product.[19]

32. The FDA will not approve an ANDA if an inactive ingredient or the composition of the proposed drug is unsafe under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug.[20]

33. *Determining bioequivalence*. An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the reference listed drug.[21] The FDCA states that a generic drug is bioequivalent to the listed drug if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[22]

34. But "for a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."[23] Thus, a showing that the active ingredient or therapeutic

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[19] *Id.* § 314.127(a)(8)(ii)(C).

[20] 21 U.S.C. 355(u)(4)(H); 21 C.F.R. §§ 314.94(a)(9)(ii), 314.127(a)(8)(i).

[21] *See, e.g.*, 21 U.S.C. § (j)(2)(A)(iv) (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 C.F.R. 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); 21 C.F.R. 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the reference listed drug referred to in the ANDA).

[22] 21 U.S.C. § 355(u)(8)(B)(i); *see also* 21 C.F.R. §§ 320.l(e) & 320.23(b).

[23] 21 U.S.C. § 355(g)(8)(C).

ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the reference listed drug, along with other information required for approval, permits the FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the reference listed drug.

35. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the reference listed drug have an impact on the rate and extent to which the active ingredient becomes available at the site of action. The statute, regulations, and case law give the FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include *in vivo* data (data from a study on human subjects), or *in vitro* data (data from laboratory studies), or both.[24] The selection of the method used to meet an *in vivo* or *in vitro* testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants are required to conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[25]

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[24] *See* 21 U.S.C. § 355(j)(7)(A)(i)(III); *see also Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with the discretion to determine whether in vivo or in vitro bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated approval processes").

[25] 21 C.F.R. § 320.24(a). In the preamble to the 1992 final rule, FDA explained that, depending upon the drug, it would determine the appropriate bioequivalence methodology on a case-by-case basis:

> Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is determined on a case-by-case basis, depending on the drug under study.

36. Section 320.24(b) of FDA's regulations describes preferred bioequivalence methods in the descending order of accuracy, sensitivity, and reproducibility. They include: (1) *in vivo* pharmacokinetic studies in whole blood, plasma, serum, or other appropriate biological fluid, or *in vitro* tests that have been correlated with and are predictive of human *in vivo* bioavailability data; (2) *in vivo* studies in which urinary excretion of the active moiety and, when appropriate, its active metabolites, are measured; (3) *in vivo* pharmacodynamic effect studies; (4) clinical endpoint studies; and (5) *in vitro* studies acceptable to FDA that ensure human *in vivo* availability.

37. In addition, and consistent with § 505(j)(8)(C) of the FDCA, § 320.24(b)(6) of the regulation states that the FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."[26] For some drug products, adequate methods for demonstrating bioequivalence have not yet been developed. In such cases, the FDA will not approve an ANDA.

38. The FDA's authority to make bioequivalence determinations on a case-by-case basis using *in vivo, in vitro,* or both types of data enables it to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards for

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Abbreviated New Drug Application Regulations, Final Rule, 57 FR 17950, 17972 (Apr. 28, 1992) (emphasis added).

[26] *Id.*; *see also Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009) (quoting 21 C.F.R. § 320.24(b) in upholding FDA sameness determination of generic drug product).

approval;[27] (2) permitting it to use the latest scientific advances in approving drug products;[28] (3) protecting the public by ensuring only safe effective generic drugs are approved for marketing;[29] and (4) making more safe and effective generic drugs available.[30]

39. *Principles of bioequivalence for locally-acting products*. For systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to

[27] 21 C.F.R. § 320.25(a) (stating that a "guiding principle" for the conduct of an in vivo bioavailability study is that "that no unnecessary human research should be done"); *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR 28872, 28883 (July 10, 1989) (in discussing section 320.22, stating that "the agency does not believe that Congress intended that unnecessary human research be conducted . . . if the agency concludes that bioequivalence can be demonstrated by in vitro tests, the agency proposes to require only such tests rather than in vivo studies").

[28] *Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement*, 42 FR 1624, 1629 (Jan. 7, 1977) ("As with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement.").

[29] *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992) (citing as one underlying policy of the Hatch-Waxman Amendments, to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

[30] *Id.* (purposes of Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (bioequivalence waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act," including making safe and affordable generic drugs available).

healthy volunteers.[31]

40. By contrast, a traditional *in vivo* bioequivalence study comparing the rate and extent of absorption of the active ingredient into the blood stream is usually of limited utility for locally acting, non-systemically absorbed drug products. In certain instances, therefore, the FDA has determined that an ANDA applicant for such a product may establish bioequivalence using *in vivo* studies with a clinical endpoint or endpoints. In addition, for certain locally acting, non-systemically absorbed products with formulations having the same qualitative ("Q1") and quantitative ("Q2") composition as the reference listed drug, the FDA has determined that an ANDA applicant may demonstrate bioequivalence using specified *in vitro* methods.

41. The choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug.

42. Congress intended to grant the FDA wide discretion to establish bioequivalence standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments. And the courts have recognized FDA's discretion to determine how the bioequivalence requirement should be met for a product or class of products, so long as the FDA's determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[32] Courts that have considered the FDA's bioequivalence determinations have consistently upheld the aspects of the FDA's implementation of the FDCA's

[31] 21 U.S.C. § 355(j)(8)(B); *FDA guidance for industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations* at 6 (Mar. 2003), http://www.fda.gov/downloads/UCM070124.pdf.

[32] *Sullivan*, 782 F. Supp. at 651; *see also Fisons*, 860 F. Supp. at 866-67 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion.").

bioequivalence requirements at issue in those cases.[33]

43. *Bioequivalence guidance*. In June of 2010, the FDA issued a guidance for the industry entitled "Bioequivalence Recommendations for Specific Products."[34] This guidance described the FDA's process of providing guidance to applicants on the design of bioequivalence studies for specific drug products. Prior to establishing the product-specific bioequivalence guidance mechanism outlined in the Bioequivalence Specific Product Guidance, the FDA only provided recommendations on the design of bioequivalence studies for specific products to parties who expressly requested such information.

44. The FDA periodically publishes notices in the Federal Register announcing the availability of draft, revised draft, and final versions of product-specific bioequivalence recommendations. These notices identify a comment period for draft bioequivalence recommendations.[35]

45. The FDA considers comments received on product-specific bioequivalence recommendations in developing its final recommendations. As with FDA guidance in general, these recommendations describe the FDA's "current thinking" and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Applicants following product-specific bioequivalence recommendations have an expectation that the FDA will agree that their approach to establishing bioequivalence is appropriate.[36] However, applicants may confer with the agency on use of different approaches for establishing

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[33] *See, e.g.*, Schering Corp., *supra*, at 397-400; *Fisons*, 860 F. Supp. at 867.

[34] Available at http://www.fda.gov/downloads/ucm072872.pdf.

[35] 21 C.F.R. § 10.115(d)(3) ("Although [final] guidance documents do not legally bind FDA, they represent the Agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.").

[36] *Id.*

bioequivalence.

46. Recommendations made in a draft or final guidance does not bind the FDA or the public. Further, even in the absence of product specific bioequivalence guidance, the FDA has the authority to approve a product supported by bioequivalence data that meets the statutory and regulatory requirements.

D. Economics of bioequivalent, generic drugs.

47. Because generic versions of brand name drugs contain the same active ingredients, and are determined by the FDA to be just as safe and effective as their branded counterparts, the only material differences between generic drugs and their branded counterparts are their prices and manufacturers. Because generic versions of branded products are commodities that cannot be differentiated, the primary basis for generic competition is price.

48. Typically, generics are at least 25% less expensive than their branded counterparts when there is a single generic competitor. They are 50% to 80% (or more) less expensive when there are multiple generic competitors on the market for a given brand. Consequently, the launch of a bioequivalent generic drug usually results in significant cost savings to all drug purchasers.

49. Since the passage of the Hatch-Waxman Amendments, every state has adopted substitution laws that either require or permit pharmacies to substitute generic equivalents for branded prescriptions (unless the prescribing physician has specifically ordered otherwise).

50. The combination of these factors – the regulatory interchangeability of bioequivalent generics for the brand, state substitution laws, margin incentives of pharmacies, and the like – results in the typical phenomenon that once a brand drug "goes generic," the product swiftly moves from a monopoly priced to a commodity priced item.

51. Generic competition enables all members of the proposed class to purchase generic versions of the drug at substantially lower prices, and to purchase the brand drug at a

reduced price.

52. Until a generic version of the brand drug enters the market, however, there is no bioequivalent generic drug to substitute for and compete with the brand drug, and therefore the brand manufacturer can continue to charge supra-competitive prices. Brand manufacturers, such as Allergan, are well aware of generics' rapid erosion of their brand sales. Brand manufacturers thus seek to extend their monopolies through any means possible, sometimes even resorting to illegal ones.

E. Petitions to the FDA

53. Section 505(j) of the FDCA creates a mechanism through which a person may file a petition with the FDA requesting the agency take, or refrain from taking, any form of administrative action. This mechanism is commonly referred to as a "citizen petition." These petitions, when used as intended, provide an opportunity for individuals to express their genuine concerns about safety, scientific, or legal issues regarding a product before, or after, its market entry.

54. The filing of a petition with the FDA imposes a burden on the agency. FDA regulations concerning citizen petitions require the FDA to respond to each citizen petition within 180 days of receipt. Those responses may be to approve or deny the requests, in whole or in part. The agency also may provide a tentative response with an estimate on a time for a full response.

55. Reviewing and responding to citizen petitions is a resource-intensive and time-consuming task. The FDA must research the petition's subject, examine scientific, medical, legal and sometimes economic issues. The FDA must also coordinate internal agency review and clearance of the petition response. These activities strain the FDA's limited resources.

56. The FDA's longtime practice – well-known in the pharmaceutical industry – is to withhold ANDA approval until after the agency has prepared and authorized a response to a citizen petition that bears on the subject of the pending ANDA. And its practice is often to do so regardless of the merit, or lack thereof, of the petition. The former director of the Office of Generic Drugs in the FDA's Center for Drug Evaluation and Research ("CDER") has acknowledged that it was "very rare that petitions present new issues that CDER has not fully considered, but the Agency must nevertheless assure itself of that fact by reviewing the citizen petitions."

57. All too often, brand companies seeking to delay the FDA's review and approval of pending ANDAs through abuse of the citizen petition process. Petitions by rival companies rarely raise legitimate concerns about the safety or efficacy of generic products, and, instead, only seek to preserve monopolies after the end of a statutorily granted patent or FDA exclusivity period.

58. Not only the ultimate futility, but also the timing, of these tactical filings is important: companies frequently file these citizen petitions on the eve of FDA approval of an ANDA for competing AB-rated generic drugs, even though the petitioner could have made the same arguments months, or even years, before.

59. The filing of petitions by brand companies challenging the FDA's bioequivalence standards or methods also signals the likelihood that the brand will file litigation against the FDA in the event that the FDA approves an ANDA that does not adopt the draconian terms demanded in its petition.

60. As a result, the filing of petitions by brand companies attacking FDA ANDA decision-making disrupts the FDA's ordinary course review of pending ANDAs. This can result

in delay of approval of a pending ANDA for considerable periods of time while the FDA evaluates the merits (or lack thereof) of the petition, prepares a response, and ensures that its positions are adequately prepared for the thinly-veiled threat of litigation.

61. The resulting delay of generic competition can be lucrative for an incumbent brand-name manufacturer facing impending competition from an AB-rated generic. The cost of filing a baseless citizen petition pales in comparison to the value of securing an additional period of monopoly profits.

62. Abusive and anticompetitive citizen petitions have become an increasingly common problem in the last 15 years, as brand-name companies have sought to compensate for dwindling new product pipelines.

63. The FDA has long acknowledged citizen petition abuse, stating as far back as 2005 that it had "seen several examples of citizen petitions that appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application but rather to try and delay the approval simply by compelling the agency to take the time to consider arguments raised in the petition whatever their merits and regardless of whether or not the petitioner could have made those very arguments months and months before."

64. Similarly, a former director of the Office of Generic Drugs noted that of 42 petitions raising issues about the approvability of generic products, "very few . . . have presented data or analysis that significantly altered FDA's policies. Of the 42 citizen petition responses examined, only three petitions led to a change in [FDA] policy on the basis of data or information submitted in the petition."[37] He further stated that "[i]t is very rare that petitions

[37] Statement of Gary Buehler, R.Ph, Director of the Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration before Special Committee on Aging

present new issues that CDER has not fully considered, but the Agency must nevertheless assure itself of that fact by reviewing the citizen petitions."[38]

65. The abuse of the petition process led Congress to add § 505(q) to the FDCA in 2007 through the FDA Amendments Act (the "FDAAA").[39] This section provide that the FDA shall not delay approval of a pending ANDA because of a citizen petition unless the FDA determines that a delay is necessary to protect the public health. The FDAAA does not, however, provide the FDA with additional resources that might allow it to more promptly respond to citizen petitions – meaning that a brand-name drug maker can still use the citizen petition process to delay generic approval while the FDA considers whether the company's citizen petition implicates issues of public health, regardless of whether the petition has any real merit.

66. Years after the enactment of the FDAAA, the FDA continues to have serious concerns about the abuse of the citizen petition process for anticompetitive purposes, noting in a 2012 report to Congress that "based on the petitions that FDA has seen to date . . . the agency is concerned that section 505(q) may not be discouraging the submissions of petitions that do not raise valid scientific issues and are intended primarily to delay the approval of competitive drug products." Indeed, recent studies have found that many petitions from brand-name drug manufacturers "appear to be last-ditch efforts to hold off generic competition," and that between

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United States Senate July 20, 2006, at 8 https://www.aging.senate.gov/imo/media/doc/hr161gb.pdf.

[38] *Id.*

[39] 21 U.S.C. 355(q).

2011 and 2015, the FDA denied 92% of § 505(q) citizen petitions (the type Allergan use here to delay generic entry).[40]

F. Patent Protection and Its Limits

67. Brand drug companies develop their drug patent portfolios to maximize their terms of patent protection.

68. There is a predictable pattern to the way brand drug companies develop their patent portfolios. The first group of patents in a brand drug company's portfolio for a particular drug may reflect a genuine technological breakthrough that may later contribute to the success of the drug. These initial patents usually cover the active compound in a prescription drug or a particular pharmaceutical composition.

69. After filing their applications for the initial patents, brand companies continue to seek other forms of patent protection; often filing for narrow modifications relating to specific formulations, methods of using the drugs, or processes for creating the drug products disclosed in the original patent filings. However, for these secondary patent filings, the original patents become "prior art," limiting the scope of follow-on patents that the brands may obtain. A brand may only obtain a *new* patent on a previously patented drug product if the specific feature the brand seeks a new patent for is non-obvious in light of the prior art – older patents, publications, and inventions. As the number of patent filings for the drug grows, so does the volume of prior art that a brand application must distinguish.

70. Therefore, a typical patent portfolio for a brand drug has its most significant patents issuing first. Over time, the later issued patents become increasingly narrow and more

[40] Feldman et al., *Empirical Evidence of Drug Pricing Games – A Citizen's Pathway Gone Astray*, 20 Stan. Tech. L. Rev. 39, 70 (2017); Carrier & Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 Am. U. L. Rev. 305, 332-333 Table 4 (2016).

difficult to obtain. Even if narrower coverage is obtained, these later issuing parents are more vulnerable to invalidation for covering subject matter that is old or obvious. The narrower coverage is also more easily designed around by generic competitors, thus preventing the brand from satisfying its burden of proving infringement to keep generics out of the market.

71. Because patent prosecutions before the PTO are non-adversarial, patent applicants are subject to special oaths and duties designed to protect the public's interest in the PTO's issuance of valid patents. Because patents usually enable a brand manufacturer to exclude competition and charge supra-competitive prices, it is crucial that any patent underlying a branded drug be valid and lawfully obtained.

72. To help ensure the "public interest is best served" when the PTO issues a patent, patent applications are subject to the duty of disclosure, candor, and good faith, which requires the applicant to disclose to the PTO "all information known . . . to be material to patentability," including any prior art.[41] This duty is imposed on those responsible for making the application, including each of the named inventors; each "attorney or agent who prepares or prosecutes the application"; and "other person[s] who is substantively involved in the preparation or prosecution of the application."[42]

G. The *Inter Partes* Review System

73. In 2011, Congress passed the Leahy-Smith America Invents Act ("AIA") to address a widely held concern that invalid patents were being issued and enforced, to the detriment of both innovation and the economy.

[41] *See* 37 C.F.R. § 1.56.

[42] *Id.* § 1.56(c).

74. A centerpiece of the AIA is the system of *inter partes* review. Through this system, members of the public can, for the first time, challenge improperly issued patents. In the past only those who sought to manufacture a patent protected product could challenge the patents' validity. The advent of *inter partes* review vastly expands the universe of patent challengers, ensuring that many patents that should not have been granted are challenged and invalidated. This system also creates a less expensive and more efficient venue for patent validity challenges. *Inter partes* review proceedings are overseen by technically educated judges, skilled in the sciences of a particular proceeding.

75. An *inter partes* review commences when a party – often an alleged patent infringer – petitions the Patent Trial and Appeals Board ("Board") to reconsider the PTO's issuance of an existing patent and invalidate it on the ground that it was obvious or anticipated by prior art.

76. The Board will grant such a request for an *inter partes* review only if the challenger of the patent shows "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."[43] The Board must decide the review within one year of the institution date.

77. The Board proceedings have become an exceedingly effective method of challenging improperly-granted patents: at least 84% of patents reaching a final written decision of Board validity challenges are adjudicated to have at least one invalid claim, and 69 percent have had *all claims* cancelled as invalid.[44]

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[43] 35 U.S.C. § 314(a).

[44] Steve Brachmann & Gene Quinn, *Are More than 90 Percent of Patents Challenged at the PTAB Defective?*, IP Watch Dog (June 14, 2017), http://www.ipwatchdog.com/2017/06/14/90-percent-patents-challenged-ptab-defective/id=84343/.

H. General principles

78. From this framework, some basic rules emerge.

79. First, brand drug companies may pursue only valid patents and must act with candor and forthrightness in their dealings with the PTO.

80. Second, brand drug companies may not provide false or misleading information to the FDA and then use that information to delay entry of less expensive generic medications.

81. Third, drug companies may not file patent infringement lawsuits against would-be competitors when the action has no realistic likelihood of success on the merits; the mere filing of such a lawsuit delays legitimate efforts to gain market entry.

82. Finally, patent holders may not knowingly use invalid patents as anticompetitive weapons and evade the consequences; federal policy favors prompt invalidation of improvidently issued patents.

83. Allergan broke all of these basic rules.

V. FACTS

84. The Plaintiffs allege the facts in the complaint on the basis (a) of personal knowledge as to those facts relating to it, (b) of investigation by counsel based on publicly available facts drawn from FDA and PTO records, litigation files, SEC filings and statements, and other publicly available records, and (c) the proceedings and decisions of this Court, including the ruling on the patent invalidity of the second wave patents in *Allergan, Inc. et al. v. Teva Pharmaceuticals USA, Inc., et al.*[45]

85. Allergan manufactures and sells an important dry-eye medication called Restasis. Since its launch in 2003, Allergan's Restasis has become one of the most important dry eye

[45] No. 2:15-cv-01455, ECF No. 523, at 20 (E.D. Tex. Oct. 16, 2017) ("*Allergan*").

treatments. In fact, it is one of the most commonly prescribed drugs in the world: last year, Restasis reached nearly $1.5 billion in U.S. sales alone.

86. Restasis is an emulsion treatment (a mixture of two more liquids that are normally unblendable) consisting of 0.05% by weight cyclosporin A[46] (an immunosuppressant), 1.25% by weight castor oil, 0.05% by weight pemulen (an emulsion stabilizer), 1% by weight polysorbate 80 (an emulsifier), and 2.2% by weight glycerin. Allergan has branded this emulsion as Restasis, with cyclosporin A acting as the active ingredient.

87. Dry eye is a progressive condition that occurs when the human eye fails to produce enough tears or enough of the natural oils that impede tear evaporation. The condition causes patients discomfort, including a sandy or gritty feeling in the eye, blurred vision, and infection. If left untreated, it can sometimes lead to serious complications that threaten vision.

88. Ophthalmologists used a number of different tests and indicators to diagnose and measure dry eye. One commonly used diagnostic device is the Schirmer tear test, which entails placing a strip of filter paper under a patient's eyelid and measuring how many millimeters of the paper are wetted by the patient's tears within five minutes. The Schirmer tear test can be conducted with or without an ocular anesthetic. But conducting the test with anesthesia is considered a better test of the tearing that occurs continuously and naturally in the absence of any unusual stimulation. Conducting the test without anesthesia provides a measure of normal tearing plus "reflexive tearing," i.e., tearing that results in response to an irritant in the eye, such a piece

[46] Cyclosporin A is sometimes spelled "cyclosporine" to distinguish it from other cyclosporins, such as cyclosporins B, C, and D. See U.S. Pat. No. 4,839,342, col. 3, ll. 7-11. The generic name for Restasis is cyclosporine ophthalmic emulsion, 0.05%. Therefore, this complaint refers to cyclosporin A as cyclosporin A or cyclosporine as to distinguish it from the generic name of Restasis.

of filter paper under the eyelid. Importantly, there is significant variability in Schirmer test scores depending on the circumstances in which the test is conducted. Thus, the comparison of those scores typically poses a challenge for researchers.

89. Another commonly used diagnostic device is corneal and conjunctival staining, in which a stain is placed in the eye. Particular stains can be used that highlight dry areas on the surface of the eye or rough areas of the cornea, thus allowing ophthalmologists to measure the degree of a patient's dry eye problem. This test also allows doctors to identify areas of the cornea that have been damaged by dry-eye conditions.

90. Other measures of dry eye include subjective indicators such as a sandy or gritty feeling in the eye, ocular dryness, photophobia, or a burning or stinging sensation. Overall levels of patient discomfort are also often gaged.

A. The 1990s: Allergan's Development of Restasis

91. Allergan has found its niche within the pharmaceutical industry as a developer and manufacturer of ophthalmic drugs. One of the company's long-term projects was the development of an effective dry eye treatment. Towards this end, Allergan began testing combinations of castor oil and cyclosporin A in the early 1990s.

1. The Kaswan Patent

92. But before Allergan could begin this research in earnest, it had to acquire an important patent in this space from another pharmaceutical company, Sandoz. U.S. Patent No. 4,839,342 (the "Kaswan patent") disclosed cyclosporin's potential as a dry eye treatment. The patent claimed methods for enhancing or restoring lacrimal gland tearing through topical administration of cyclosporine to the eye in a pharmaceutically acceptable vehicle. The Kaswan patent also recited use of castor oil, among other compounds, as a pharmaceutically acceptable vehicle for delivery of cyclosporine to the eye.

93. In 1993, Allergan bought a license from Sandoz to use that patent, and commenced testing various formulations of cyclosporin A.

94. One of the major challenges Allergan's scientists confronted was how to deliver cyclosporine to the eye. Cyclosporin A is highly insolubility in water, and therefore very difficult to deliver in an aqueous solution. Developing an appropriate vehicle for the delivery of cyclosporine to the eye posed a significant hurdle.

95. Allergan eventually solved this problem by developing an oil-in-water emulsion that contained a small amount of castor oil (a hydrophobic vehicle that would dissolve the cyclosporine A), together with an emulsifier and an emulsion stabilizer in water.

96. Allergan disclosed this achievement in two patents.

2. The Ding I Patent

97. On December 12, 1995, the PTO issued U.S. Patent No. 5,474,979 ("the Ding I patent"). This patent disclosed Allergan's cyclosporine A/castor oil emulsion. More specifically, the patent claimed a pharmaceutical emulsion consisting of between about 0.05% and about 0.4% by weight cyclosporine A; between about 0.625% and about 0.4% by weight castor oil; about 1% by weight polysorbate 80 (an emulsifier); about 0.05% by weight Pemulen (an emulsion stabilizer); and about 2.2% by weight glycerin. The Ding I patent described this emulsion as having a "high comfort level and low irritation potential"[47] as well as long-term stability.[48]

[47] Ding I patent col. 1, ll. 8-9.

[48] *Id.* col. 3, ll. 58-63.

98. The patent also specified four examples of the claimed invention. The table below, which appeared as Example 1 of the Ding I patent,[49] disclosed multiple potential formulations for the castor oil and cyclosporin A emulsion. For example, the formulation labeled D consisted of 0.1% cyclosporin A and 1.25% castor oil, while E contained 0.05% cyclosporine and 0.625% castor oil.

Example 1

	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen ®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6	7.2–7.6

99. The Ding I patent further stated that the preferred weight ratio of cyclosporine A to castor oil was below 0.16 (which is the maximum solubility level of cyclosporine A in castor oil) and the more preferred weight ratio of cyclosporine A to castor oil was between 0.02 and 0.12.

100. The formula Allergan eventually settled on and sold as Restasis falls within the range of values disclosed and claimed in the Ding I patent.

3. The Ding II Patent

101. On November 9, 1999, Allergan obtained a second patent related to ocular emulsions. U.S. Patent No. 5,981,607 ("the Ding II patent") claimed a method of alleviating dry-eye-related symptoms by topically applying an emulsion of a higher fatty acid glyceride,

[49] *Id.* col. 4, ll. 31-43.

polysorbate 80, and an emulsion-stabilizing amount of Pemulen in water to the ocular tissue.[50] The Ding II patent further claimed an emulsion where the higher fatty acid glyceride was castor oil, in an amount between about 0.625% by weight and about 5% by weight.[51]

4. The Phase 2 Trial and Stevenson Paper

102. In the late 1990s, after Allergan filed for these patents, Allergan began clinical trials of several combinations of cyclosporin and castor oil. In the first clinical trial (the "Phase 2" study), Allergan tested four of the combinations listed in Example 1 of the Ding I patent: 0.05% cyclosporin with 0.625% castor oil; 0.1% cyclosporin with 1.25% castor oil; 0.2% cyclosporin with 2.5% castor oil; and 0.4% cyclosporine with 5% castor oil (Examples 1A, 1C, 1D, and 1E in the Ding I patent) for three months. A number of different tests were used to measure patient improvement including rose bengal staining and Schirmer tear tests *without anesthetic*. The study also measured subjective indicators of dry eye, such as ocular itching, burning, blurred vision, foreign body sensation, dryness, photophobia, and soreness or pain.

103. As is typically the case, the goal of the Phase 2 study was only to determine the safety and efficacy of particular doses of the drug so that researchers could settle on an appropriate dosage level for subsequent large-scale Phase 3 clinical studies. The Phase 3 studies would then be used to support Allergan's application to the FDA to market the drug.

104. A 2000 journal article by Dara Stevenson, Joseph Tauber, and Brenda L. Reis ("Stevenson") reported the results of Allergan's Phase 2 trial.[52] The Stevenson paper reported

[50] Ding II patent, col. 9, ll. 2-7.

[51] *Id.* col. 10, ll. 4-10.

[52] Dara Stevenson, Joseph Tauber, & Brenda L. Reis, *Efficacy and Safety of Cyclosporine A Ophthalmic Emulsion in the Treatment of Moderate-to-severe Dry Eye Disease: A Dose-Ranging, Randomized Trial*, 107 Ophthalmology 967 (May 2000).

that a total of 88 patients with moderate-to-severe dry eye disease completed the Phase 2 trial: 16 in a castor-oil-only control, group; 17 in the 0.05% group; 18 in the 0.1% cyclosporin group; 20 in the 0.2% cyclosporin group; and 17 in the 0.4% cyclosporin group.[53] Stevenson did not disclose the percentage of castor oil in each formulation, but it disclosed that the amount of castor oil increased relative to the cyclosporin present so that all of the cyclosporin was dissolved.[54]

105. The paper concluded that all tested concentrations significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease and mitigated dry eye disease's effects on vision-related functioning. And all outperformed the castor-oil-only control group. Furthermore, the paper reported that all tested concentrations were safe and effective in increasing tearing in certain patient groups.

106. Critically, Stevenson concluded that there was *no clear dose-response relationship* between the 0.05% cyclosporin formulation and formulations containing greater amounts of cyclosporin. In other words, the drug's efficacy did not increase when more than 0.05% cyclosporin A (the active ingredient) was present. Put another way, the Stevenson paper concluded that the 0.1% cyclosporin formulation *did not perform better* than the 0.05% cyclosporine formulation.

107. The study did note, however, that the 0.1% cyclosporine formulation "produced the most consistent improvement in objective and subjective endpoints (such as superficial punctate keratitis and rose bengal staining)," while the 0.05% cyclosporine formulation "produced the most consistent improvements in patient symptoms (such as sandy/gritty feeling

[53] *Id.* at 970.

[54] *Id.* at 968.

and ocular dryness)."[55] Therefore, Stevenson suggested "that subsequent clinical studies should focus on the cyclosporine 0.05% and 0.1% formulations."[56]

5. The Phase 3 Trial and Sall Paper

108. Allergan's Phase 3 trials did just that: the trials compared the efficacy and safety of a 0.05% cyclosporine / 1.25% castor oil formulation to that of a castor-oil-only vehicle and the safety and efficacy of a 0.1% cyclosporine / 1.25% castor oil formulation to that of a castor-oil-only vehicle.

109. Allergan conducted the two separate Phase 3 trials simultaneously: 235 patients were given a formulation containing 0.05% cyclosporin / 1.25% castor oil; 218 patients were given another containing 0.1% cyclosporin / 1.25% castor oil; and 218 were given a castor-oil-only control vehicle for 6 months. Thus, the Phase 3 trial (671 patients total) contained nearly *eight times* the number of patients in the Phase 2 trial (88 patients total). Like the Phase 2 study, these Phase 3 trials measured patient improvement through a number of different tests and indicators including corneal staining and Schirmer tear tests. However, unlike in the Phase 2 study, the Schirmer tear tests in the Phase 3 trials were conduct *with* and *without* an anesthetic. The trials also measured subjective indicators of ocular discomfort, such as stinging/burning, itching, sandiness/grittiness, blurred vision, dryness, light sensitivity, pain or soreness. These tests and symptoms were checked at one, three, four, and six months.

110. A 2000 published paper by Kenneth Sall, Dara Stevenson, and others reported the

[55] *Id.* at 974.

[56] *Id.*

results of the Phase 3 trials ("Sall").[57]

111. This paper concluded that both cyclosporine formulations (0.1% and 0.05% cyclosporin) were more effective than the castor-oil-only vehicle in treating dry eye (though the castor oil vehicle also produced significant improvements over the patient's baseline, suggesting that it was a contributing factor to the formulations' success). Once again, the paper reported *no dose-response effect* between the 0.05% cyclosporine / 1.25% castor oil formulation and the 0.1% cyclosporine / 1.25% castor oil formulation. In other words, the Sall paper found that the 0.05% cyclosporin formulation *was not superior* to the 0.1% formulation, and vice versa.

112. The Sall paper emphasized that the purpose of the two Phase 3 trials was to compare the efficacy and safety of the 0.05% and 0.1% cyclosporin formulations *to the control*. In other words, the purpose of these trials was *not* to compare the 0.05% cyclosporine formulation to the 0.1% cyclosporin formulation directly, but rather to compare those formulations to the *castor oil only vehicle*.

113. At three months, the paper reported a statistically significant difference between the 0.05% cyclosporin group and the patient's baseline score (scores without treatment) on the categorized Schirmer tear test with anesthesia. At six months, both the 0.05% cyclosporin group and the 0.1% cyclosporin group showed statistically significant improvements compared to the patients' baseline on that test. Sall also reported that at month 3 there was a statistically significant difference between the 0.05% cyclosporin group and the castor-oil only control, but not a statistically significant difference between the 0.05% cyclosporin group and the 0.1% group.

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[57] Kenneth Sall, et al., *Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease*, 107 Ophthalmology 631 (2000).

6. FDA Approval of Restasis

114. In February 1999, following the Phase 3 trials, Allergan filed a NDA with the FDA seeking authorization to market the 0.05% cyclosporine formulation tested in those trials. The proposed commercial product – Restasis – would contain all of the components of that formulation, including 1.25% castor oil.

115. In December 2002, the FDA approved the application, authorizing the sale of Restasis as "a topical immunomodulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca."[58]

116. In 2003, following approval, Allergan launched Restasis.

B. The 2000s: Allergan's Procurement of the Second Wave Patents

117. For over a decade following the approval of Restasis, Allergan filed a variety of patent applications attempting to claim combinations of castor oil and cyclosporine. Allergan did this notwithstanding the Ding I & II patents, which claimed the range of formulations within which Restasis fell, and the Stevenson and Sall studies, which demonstrated there were no statistical differences in outcomes between the 0.05% and 0.01% cyclosporine formulations.

1. September 2003 and August 2004: Allergan files new patent applications on Restasis.

118. On September 15, 2003, Allergan filed a provisional application (a placeholder): U.S. Patent Application No. 60/503,137 ("the '137 application). Allergan followed up this application a year later, on August 27, 2004, with application No. 10/927,857 ("the '857 application"). These applications were directed to methods and compositions for treating dry eye

[58] *Allergan* at 17.

by administering an emulsion composed of a hydrophobic component (such as castor oil) and a cyclosporin component of less than 0.1% by weight. The ’857 application further specified that the weight ratio of the cyclosporin component to the hydrophobic component should be less than 0.08. Dependent claims in the application recited a hydrophobic component, such as castor oil, in an amount greater than 0.625% of the composition. Thus, the application claimed subject matter encompassed by the Ding I patent.

2. January 2007: The PTO examiner rejects the ’857 application.

119. On January 17, 2007, the PTO examiner rejected the ’857 application. After Allergan withdrew a number of the application’s claims, the examiner concluded that the remaining claims would have been obvious in light of Ding I. As the examiner explained, it was obvious to try a 0.05% cyclosporine / 1.25% castor oil formulation because that ratio fell within the limit range of ratios claim in the Ding I patent.

120. In response, Allergan amended the ’857 application to include a claim to an emulsion of water, 1.25% castor oil, and 0.05% cyclosporine, *i.e.*, Restasis. But the PTO examiner again rejected the application.

121. Allergan then appealed the rejection. While the appeal was pending, Allergan filed a continuation of the ’857 application: U.S. Patent Application No. 11/897,177 (“the ’177 application”). The ’177 application was similar to the ’857 application, but added claims regarding new conditions that the method was asserted to treat, including corneal graft rejection.

3. June 2009: Allergan concedes that the claims of the ’857 application would have been obvious in light of Ding I.

122. Nonetheless, in June 2009, Allergan completely reversed course and conceded in writing that the ’857 application was obvious in light of Ding I. And Allergan made a similar concession with respect to the ’177 patent. Specifically, Allergan wrote to the PTO:

> The applicants concede that it would have been obvious to modify examples 1A-1E of the Ding reference to arrive at [the Restasis formula]. *The differences are insignificant.* One need only use the cyclosporin concentration of Example 1E (0.05%), the castor oil concentration of Example 1D (1.250%), and the remaining ingredients of those examples. As the examiner correctly observes, one of ordinary skill in the art "would readily envisage" such a composition, especially in view of Example 1B: having selected 0.05% as the concentration of cyclosporin, Example 1B (wherein the ratio of cyclosporin to castor oil is 0.04) teaches that the concentration of castor oil should be 1.25% (0.05% / 1.25% = 0.04). The applicants concede that in making this selection (0.05% cyclosporin and 1.25% castor oil) there would have been a reasonable expectation of success; the differences between Examples 1A-1E and Composition II are too small to believe otherwise.
>
> The formulation of Composition II is squarely within the teaching of the Ding reference, and the Office should disregard any statements by the applicants suggesting otherwise, whether in this application or in co-pending application no. 11/897,177.[59]

123. Thus, Allergan admitted that the "differences" between Restasis and the Ding I examples "[were] insignificant"; that in "select[ing]" the Restasis formula (0.05% cyclosporin and 1.25% castor oil), "there would have been a reasonable expectation of success"; the "differences between" the Ding I patent examples and the Restasis formula "are too small to believe otherwise"; and the composition claims advanced by the '857 and '177 applications were "squarely within the teaching of the Ding reference."[60] In its concession, Allergan also included a table demonstrating *exactly how* Restasis would be "readily envisage[d]" based on Examples 1B, 1D, and 1E of the Ding I patent:

[59] *Id.* at 19.

[60] *Id.*

Compositions of the Ding reference compared to

Composition II of the present application

	Ding *et al.* Example 1B	Ding *et al.* Example 1D	Ding *et al.* Example 1E	Composition II
Cyclosporin A	0.20 %	0.10 %	**0.05 %**	**0.05 %**
Castor Oil	5.00 %	**1.250 %**	0.625 %	**1.250 %**
Polysorbate 80	1.00 %	1.00 %	1.00 %	1.00 %
Pemulin®	0.05 %	0.05 %	0.05 %	0.05 %
Glycerine	2.20 %	2.20 %	2.20 %	2.20 %
NaOH	qs	Qs	qs	qs
Purified water	qs	Qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6
cyclosporin : castor oil	**0.04**	0.08	0.08	**0.04**

124. Allergan then withdrew its pending appeal and canceled all of the ’857 application’s pending claims.

125. Nonetheless, it added a new claim to the application: a composition in which the amount of cyclosporin was less than 0.05% and the ratio of cyclosporin to castor oil was less than 0.04.

126. On September 1, 2009, the examiner rejected this new claim as obvious in light of Ding I.

127. By April 2011, the PTO issued a notice of abandonment on the ’857 application to Allergan. (On December 21, 2013, the ’177 application issued as U.S. Patent No. 8,618,064, but this patent was narrowly limited to use of a cyclosporine formulation to treat corneal graft rejection).

128. Thus, from the launch of Restasis in 2003 until mid-2013, the only patent protecting Restasis was the Ding I patent. That patent was set to expire in May of 2014.

4. June 2013: The FDA issues the draft guidance for generic cyclosporine emulsions.

129. In June 2013, with the Ding I patent's expiration date on the horizon, the FDA issued a draft guidance containing recommendations to applicants seeking to gain approval of ANDAs for generic versions of Restasis. Such guidance was consistent with long-standing practice of the FDA as a science-driven agency.

130. Neither draft nor final guidance are required for the FDA to approve an ANDA. The FDA often approves ANDAs in situations where it has issued no guidance at all, or where it has issued guidance only in draft form. But the posting of a draft guidance, and seeking comment on it, shows the FDA is well underway in evaluating the circumstances under which it would approve an ANDA for a particular product. As a result, the June 2013 issuance of the draft guidance for cyclosporine emulsion ophthalmic products was a clear signal to the drug industry that the FDA was actively considering the circumstances under which would accept for filing, and approve, ANDAs for generic Restasis.

131. Under the June 2013 draft guidance, the FDA recommended the use of specified *in vitro* testing where the quality (Q1) and quantity (Q2) of the proposed ingredients of the generic were the same as that used for Restasis. (In vivo testing was recommended where they were not, and in other circumstances).

132. Because *in vitro* testing is often far less costly, time-consuming and invasive than in vivo testing, posting of the draft guidance in June 2013 also signaled that would-be competitors to Allergan's Restasis brand product might well be in the position to gain ANDA approvals of cyclosporine ophthalmic emulsion, 0.05% products by May of 2014, i.e., upon expiration of the *Ding I* patent.

133. To qualify for the *in vitro* option for cyclosporine emulsion products pursuant to

21 CFR § 320.24(b)(6) (under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence of a drug product), all of the following criteria must be met: (i) the test and reference listed drug formulations are qualitatively and quantitatively the same (Ql/Q2); (ii) acceptable comparative physicochemical characterization of the test and reference listed drug formulations must be performed on seven separate, specified dimensions, and; (iii) acceptable comparative in vitro drug release rate tests of cyclosporine from the test and reference listed drug formulations.

134. An *in vivo* BE study with clinical endpoint is requested for any generic cyclosporine ophthalmic emulsion, 0.05% that has a different inactive ingredient, a difference of more than 5% in the amount of any inactive ingredient compared to that of the reference listed drug, or unacceptable data from in vitro comparative studies. The FDA pointed out that a bioequivalence study with clinical endpoints for cyclosporine ophthalmic emulsions may not be feasible or reliable due to the modest efficacy demonstrated by Restasis. For that reason, the draft guidance recommended that any sponsor electing to conduct such a study submit the study protocol for review.

135. The FDA solicited public comments on this draft guidance.

136. On August 17, 2013 – and despite the exacting and comprehensive approach that the FDA was taking to proposed cyclosporine ophthalmic emulsion products (that for in vitro testing to be adequate, both active and inactive ingredients be the same, and that there be similarity along 7 physiochemical characteristics) – Allergan submitted a lengthy comment to the agency asserting that the FDA could not approve any Restasis ANDA relying on *in vitro* testing. It told the FDA it should "replace the Draft Guidance with a revised guidance document that

explains in vivo comparative clinical studies are required to demonstrate that a proposed generic product is bioequivalent to" Restasis.[61]

137. Allergan caused its radical position to be echoed by comments submitted by several doctors who, unbeknownst to the FDA, had received payments from Allergan for "consulting" services and "travel and lodging," generally and specifically relating to Restasis. For example, Dr. Stephen Pflugfelder, who submitted a comment on August 8, 2013[62] critical of an *in vitro* bioequivalence option, received roughly $70,000 in payments from Allergan in 2013.[63] Similarly, on September 3, 2013,[64] Dr. Jai G. Parekh posted a comment raising similar concern with the bioequivalence issue; neither he nor Allergan disclosed to the FDA that Allergan paid him nearly $9,000 in 2013 for his services relating to Restasis and other drugs.[65] Dr. Marc Bloomenstein's comment, posted August 15, 2013,[66] raising similar alarm, failed to disclose payments from Allergan in 2013, amounting to $47,665, all but two of which explicitly relate to Restasis.[67]

[61] Allergan, Inc., Comment re Docket No. FDA-2007-D-0369: June 2013 Draft Bioequivalence Guidance for Cyclosporine Ophthalmic Emulsion, 0.05% (Aug. 17, 2013) at 1.

[62] Comment re Docket No. FDA-2007-D-0369-0236.

[63] *See* ProPublica, Dollars for Docs: Stephen C Pflugfelder, https://projects.propublica.org/docdollars/doctors/pid/356009 (last visited Dec. 29, 2017).

[64] Comment re Docket No. FDA-2007-D-0369-0246.

[65] *See* ProPublica, Dollars for Docs: Dr. Jai Parekh, https://projects.propublica.org/docdollars/doctors/pid/37605 (last visited Dec. 29, 2017).

[66] Comment re Docket No. FDA-2007-D-0369-0239.

[67] *See* ProPublica, Dollars for Docs: Dr. Marc Bloomenstein, https://projects.propublica.org/docdollars/doctors/pid/25861 (last visited Dec. 29, 2017).

5. August 2013: Allergan renews its gambit to obtain secondary patents.

138. On the heels of the FDA's draft guidance and with the Ding I patent's expiration looming, Restasis decided to renew its attempt to obtain secondary patents on the Restasis formulation.

139. In August 2013, Allergan filed six continuation applications derived directly or indirectly from the '177 application. These six additional applications were identical to the previous failed applications with only minor variations in a few: Allergan added four sentences to three of the applications' specifications that further described the role of cyclosporine as an immunosuppressant and the conditions that may be treated with cyclosporine.

140. As the *Allergan* court would later explain its decision invalidating the patents that resulted from these applications, "[t]he new applications were intended to protect the Restasis composition and the method of using that composition in treating dry eye and KCS after the expiration of the Ding I patent in 2014."[68]

141. But before prosecuting these new applications, Allergan had to claw back its prior concession that the Restasis formulation was obvious in light of Ding I.

142. Under patent law, "where there is a range disclosed in the prior art, and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges."[69] In such circumstances, to overcome a rejection for obviousness, a patent application must "come forward with evidence

[68] *Id.* at 20.

[69] *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1304-05 (Fed. Cir. 2015).

that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.'"[70]

143. This was exactly the situation Allergan found itself: a prior art patent disclosed a finite range, and prior studies showed that there was motivation to select the Restasis formulation from that range. Therefore, to escape the inevitable conclusion of obviousness, Allergan would have to show some sort of an "unexpected result."

144. To do so, in its August 2013 PTO filings Allergan represented that "since [the concession was filed], the Applicants have collected evidence that supports the patentability of the pending claims." Crucially, Allergan told the PTO that its reasserted claims were patentable because Restasis's particular formulation – 0.05% cyclosporin / 1.25% castor oil – performed far better than would be expected as compared to the 0.1% cyclosporine / 1.25 % castor oil formulation. More specifically, Allergan claimed that the Phase 2 trial revealed that the 0.1% formulation outperformed the 0.05% cyclosporine formulation, while the Phase 3 study revealed the 0.05% formulation outperformed the 0.1% formulation. Thus, the results of the Phase 3 trial were unexpected in light of the Phase 2 results.

145. The representations were false.

146. The data – published 13 years earlier in the Stevenson and Sall papers – bore out none of Allergan's claims. The Stevenson and Sall papers both concluded that there was *no dose-response effect* between the 0.05% cyclosporine and the 0.1% cyclosporine castor oil formulations. *Neither trial* showed a scientifically significant difference between the two formulations: the Phase 2 trial did not suggest the 0.1% cyclosporine formulation was superior, and the Phase 3 study did not suggest the 0.05% cyclosporin formulation was more effective.

[70] *Id.* at 1305.

147. The *Allergan* court later explained this reality in painstaking detail in its opinion invalidating the second wave patents.

148. As the Court summarized, the Phase 2 data presented in Stevenson reported results on 14 efficacy measures: rose bengal staining (temporal), rose bengal staining (nasal), corneal staining, Schirmer scores without anesthesia, tear film debris, tear break-up time, artificial tear use, OSDI score, stinging or burning, itching, sandy or gritty feeling, dryness, light sensitivity, and pain. And these efficacy measures were observed at five different points in time: week 4, week 8, week 12, post-treatment week 2, and post-treatment week 4.

149. Accurate analysis of this data revealed that the 0.05% and 0.1% formulations were statistically significant for only *2* of the *58 measured categories*. As the *Allergan* court concluded, "those two individual points of statistical significance, out of all of the tested categories and time points, are [in]sufficient to demonstrate a real difference in effectiveness between the 0.05% and 0.1% cyclosporin formulations."[71]

150. As for the Phase 3 study, 21 efficacy measures were observed: corneal staining, temporal conjunctival staining, nasal conjunctival staining, the sum of temporal and nasal conjunctival staining, the sum of corneal and conjunctival staining, raw Schirmer scores with anesthesia, categorized Schirmer scores with anesthesia, raw Schirmer scores without anesthesia, categorized Schirmer scores without anesthesia, OSDI score, facial expression subjective rating scale, stinging or burning, itching, sandy or gritty feeling, blurred vision, dryness, light sensitivity, pain, global evaluation of response to treatment, treatment success, and artificial tear use. Those efficacy markers were measured at four points: 1 month, 3 months, 4 months, and 6 months.

[71] *Allergan* at 51.

151. For this trial, at least 71 of the 80 total data points showed no statistically significant difference between the two cyclosporin formulations. Thus, as the *Allergan* court concluded, "the overwhelming bulk of the data (71 out of 80 data points) supports an inference that the two cyclosporin formulations performed similarly, and an even larger portion of the data (76 out of 80 data points) supports an inference that the 0.05% cyclosporin formulation did not perform better than the 0.1% cyclosporin formulation."[72]

152. The Court summarized, "there is a dearth of evidence showing any real difference between the efficacy of the 0.05% and 0.1% cyclosporine formulations in Phase 2, as presented in Stevenson, and in Phase 3, as presented in Sall. A person of skill reviewing those papers would come to the conclusion that neither formulation was more effective than the other in Phase 2. That person of skill would reach the same conclusion for Phase 3."[73]

153. In short, the Phase 2 study did not suggest the 0.1% cyclosporine formulation was superior to the 0.05% cyclosporine formulation, and the Phase 3 study did not suggest that that the 0.05% formulation was superior to the 0.1% formulation in Phase 3. The basis for Allergan's claim to patentability – that the Phase 2 trial favored the 0.1% formulation, and then the Phase 3 trial *unexpectedly* favored the 0.05% formulation – is not born out by the results of *either* the Phase 2 trial *or* the Phase 3 trial.

154. Allergan was aware of this reality and even admitted it to the FDA when Allergan initially presented the results of the Phase 3 trial to the agency: "Upon presenting the Phase 3 results to the FDA, Allergan explained that the performance of the 0.05% cyclosporin formulation was not surprising because the lack of a dose response – i.e., the similar level of

[72] *Id.* at 67.

[73] *Id.* at 73.

efficacy for formulations containing 0.05% or more of cyclosporin – was observed earlier in Phase 2."[74] In fact, Allergan had initially decided to test the 0.05% formulation in the Phase 3 study because the FDA had suggested that formulation given the lack of dose response above 0.05% cyclosporin in Phase 2: "*[b]ecause we did not show a clear differentiation in effect among the doses [in Phase 2]*, it was recommended [by the FDA] that we include a lower concentration [0.05% cyclosporin] in one Phase 3 clinical trial to confirm that we have chosen the lowest effective concentration."[75]

155. The *Allergan* court further pointed out that Allergan's attempt to contort the Phase 2 trial into a study of the comparative efficacy of the 0.05% and 0.1% cyclosporin formulations, in-and-of-itself, constitutes a fundamental flaw. As explained earlier, it was *the Phase 3 studies*, not *the Phase 2 study*, that were intended to aid selection between the 0.05% and 0.1% cyclosporin formulations. With only 88 participants, the Phase 2 study was not designed to reveal statistically significant differences between the various tested formulations. As the *Allergan* court observed, "[t]he small size of the Phase 2 study makes it difficult to draw reliable conclusions about the relative efficacy of different formulations."[76] Instead, the 671-person Phase 3 study was design to accomplish that goal. Accordingly, Allergan's effort to convert the Phase 2 study into an assessment of the relative efficacy of the 0.05% and 0.1% cyclosporin formulations in order to contrast it with the Phase 3 study "lies at the heart of the problem with its 'unexpected results' analysis."[77] The Phase 2 study was never meant to compare the two

[74] *Id.* at 59-60.

[75] *Id.* at 60.

[76] *Id.* at 46

[77] *Id.* at 45.

different formulations. Therefore, Allergan should never have relied on this study to assert the 0.1% formulation performed better than the 0.05% formulation in the first place.

156. Because Ding I discloses the narrow range of formulations within which Restasis falls, Allergan could only escape a conclusion of obviousness by showing unexpected results. But the Phase 2 testing was neither designed to show, nor suggested, that the 0.1% formulation was superior to the 0.05% formulation. And the Phase 3 similarly failed to show a dose response or preferential efficacy between dosages. Furthermore, the two studies, Phases 2 and 3, could not properly be compared to each other. Allergan's own conclusion – 13 years earlier – that there was nothing unexpected in the Phase 3 results, was the truth. Allergan's representations to the contrary were false.

157. In October 17, 2013, the patent examiner rejected all Allergan's second wave patent applications, once again relying heavily on the Ding I patent.

6. October 23, 2013: Allergan submits a highly misleading declaration – the Schiffman declaration – to overcome the examiner's rejection.

158. On October 23, 2013, Allergan submitted a declaration from Dr. Rhett M. Schiffman claiming that test results showed the Restasis formulation (0.05% cyclosporine / 1.25% castor oil) produced new and unexpected results relative to the 0.05% cyclosporine / 0.625% castor oil and 0.1% cyclosporine / 1.25% castor oil formulations recited in the Ding I patent. Specifically, Allergan relied on Dr. Schiffman's declaration to claim:

> [S]urprisingly, the claimed formulation [of 0.05% cyclosporine and 1.25% castor oil] demonstrated an *8-fold* increase in relative efficacy for the Schirmer Tear Test score in the first study of Allergan's Phase 3 trials compared to the relative efficacy for the 0.05% by weight cyclosporine A/0.625% by weight castor oil formulation discussed in Example 1E of Ding, tested in Phase 2 trials. . . . [T]he claimed formulations also demonstrated a *4-fold* improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a *4-fold* increase in relative efficacy for decrease in corneal staining score in both of

> the Phase 3 studies compared to the 0.05% by weight cyclosporine A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E). *This was clearly a very surprising and unexpected result.*

In plain English, Dr. Schiffman declared that the Schirmer tear test scores for the 0.05% cyclosporine / 1.25% castor oil formulation (Restasis) in the first Phase 3 trial revealed that 0.05% cyclosporine formulation resulted in an *8-fold* increase in efficacy over the 0.05% cyclosporine / 0.625% castor oil formulation tested the Phase 2 trial (and disclosed in Ding I). Dr. Schiffman further claimed, based on the Schirmer tear test scores in the second Phase 3 trial and the corneal staining tests results in both Phase 3 trials, that the Restasis formulation showed a *4-fold* improvement over the 0.05% cyclosporine / 0.625% castor oil formulation tested in Phase 2. According to Allergan and Dr. Schiffman, these results were surprising because the Phase 2 trial had suggested the 0.1% cyclosporine formulation was superior to the 0.05% formulation.

159. Dr. Schiffman's representations to the PTO were false and misleading. As the *Allergan* court explained in its invalidity decision, Dr. Schiffman's declaration is unreliable as basis for patentable for four principle reasons.

- *First*, Dr. Schiffman relied on statistically insignificant data to draw his conclusions and then *concealed* the data's statistical insignificance from the PTO. Scientists do not rely on statistically insignificant data for an obvious reason: such data is unreliable.

- *Second*, Dr. Schiffman did not compare like test results; he compared the results of Schirmer tear tests performed *with* anesthetic to Schirmer tear tests conducted *without* the anesthetic. Such a comparison has no scientific value.

- *Third*, Dr. Schiffman used data manipulation technics to amplify small differences between test results. Such contortions gave the PTO the false impression that Dr. Schiffman had actually obtained significant results.

- *Fourth*, Dr. Schiffman failed to tell the PTO that he lifted the data he presented *from the Sall paper*. Thus, his data was not only over a decade old, it was also

> *prior art* to the second wave Restasis patents. As such, this data could not support Allergan's patent application.

In short, as the *Allergan* court concluded, "Dr. Schiffman's declaration and the accompanying exhibits painted a false picture."[78]

a. Dr. Schiffman relied on statistically insignificant data.

160. First, Dr. Schiffman improperly relied on statistically insignificant data to draw his desired conclusions: he disregarding the error bars and p-values associated with the data he lifted from the Sall study.

161. A p-value is the probability that a given outcome is result of random chance. P-values are critical because they tell scientists whether a given result is statistically significant, *i.e.*, whether it should be taken seriously. P-values are calculated through head-to-head comparisons (pair-wise comparison) of the mean values of two groups of data. For example, one could compare (a) the mean improvement in Schirmer scores over a three-month period for patients treated with the 0.05% cyclosporine formulation to (b) the mean improvement in Schirmer scores over a three-month period for patients treated with the 0.1% cyclosporine formulation. A pair-wise comparison of those two means could be used to derive a p-value indicating whether there was a real difference between the average improvement in Schirmer scores for the 0.05% cyclosporine formulation and the average improvement in Schirmer scores for the 0.1% cyclosporine formulation. A small p-value, such as $p = 0.05$, would indicate that the observed difference between those averages is meaningful, in that the difference is the result of random chance only 5% of the time. A large p-value, such as $p = 0.30$, would mean that the observed difference is the result of random chance 30% of the time. Scientists typically regard a

[78] *Allergan* at 82.

p-value of 0.05 as the cut off for statistical significance: data with p-values much higher than 0.05 are disregarded.

162. Dr. Schiffman omitted the p-values associated with the raw data he took from the Sall paper in an attempt to pass off statistically insignificant differences between the 0.05% and 0.1% cyclosporin formulations as important. In reality, and as the *Allergan* court explained, "[n]one of the pair-wise comparisons between the two cyclosporine formulations for corneal staining and Schirmer scores in the Phase 2 study or the pooled Phase 3 studies demonstrated statistical significance at any time point."[79]

163. In fact, many of the p-values for the pair-wise comparisons were very high. For example, the p-values for a comparison of Schirmer scores without anesthesia in Phase 2 – the only p-value regarding Schirmer scores that were calculated in Phase 2 – was 0.651 at week 4, 0.790 at week 8, and 0.834 at week 12. No scientist would take seriously the differences in the raw data results between the two cyclosporine formulations given these extremely high p-values. These p-value essentially communicated that any measured difference in the efficacy of the two formulations was more likely-than-not a result of random chance. Interpreted properly, the data Schiffman told the PTO showed "unexpected results" actually showed no significant difference in efficacy between the 0.05% and 0.1% formulation.[80]

164. When Dr. Schiffman was questioned about this misrepresentation during the second wave patents' validity trial, all he could muster was: "I think we're making – in a sense,

[79] *Id.* at 76.

[80] *Id.* at 133.

we're trying to make too much out of statistical techniques when the bigger picture is – is – is really sufficient, I think."[81]

165. As the *Allergan* court explained, "statistical significance is an important component in establishing the reliability of the clinical data for a person of skill in the art."[82] Indeed, the lack of statistical significance between the two formulations is what kept Stevenson, et al., from concluding, in their peer-reviewed paper, that the 0.1% formulation did best or that the 0.1% formulation did better than 0.05%. As Allergan's expert conceded at trial, "one point of peer review is to make sure that authors don't overstate their case."[83]

b. Dr. Schiffman did not compare like test results.

166. Second, in addition to Dr. Schiffman's deliberate concealment of the p-values associated with the data he presented, Dr. Schiffman also did not disclose to the PTO that Phase 2 and 3 test results he compared to demonstrate that the 0.05% cyclosporine formulation performed better than the 0.1% formulation in Phase 3 *came from two distinct types of tests.* In his declaration, Dr. Schiffman compared test scores from Schirmer test performed *without* anesthesia in Phase 2 to Schirmer test scores performed *with* anesthesia in Phase 3. Schirmer tear testing *with* anesthesia measures the baseline level of tearing; Schirmer tear testing *without* anesthesia measures baseline tearing plus some level of reflective tearing based on the patient's reaction to the filter paper used to give the test. Therefore, Schirmer tear tests *without* anesthesia will inherently measure more tearing than Schirmer tear testing *with* anesthesia. Thus, comparing a Schirmer tear test without anesthesia to one with is akin to comparing the marathon time of a

[81] *Id.* at 76.

[82] *Id.* at 59.

[83] *Id.*

runner who ran an easy course in good conditions to the time of runner on a harder course with worse conditions to determine the faster runner. In reality, the Schirmer tear test results *without* anesthesia in Phase 3 showed a trend similar to the Schirmer tear test results *without* anesthesia in Phase 2 in that both favored the 0.1% cyclosporine formulation, not the 0.05% cyclosporine formulation. But neither Schiffman nor Allergan disclosed this fact to the PTO.

167. Instead, Schiffman's declaration only evaluated the Schirmer tear test results *with* anesthesia in Phase 3, which significantly favored the 0.05% cyclosporine formulation. Relying on his skewed comparison, Schiffman told the PTO that 0.05% cyclosporine formulation (the Restasis formulation) "demonstrated an *8-fold* increase in relative efficacy" as compared to the 0.1% formulation. Only through his manipulation of the data – comparing the results of two different types of dry eye test – was Dr. Schiffman was able to suggest that the 0.05% cyclosporine / 1.25% castor oil formulation tested in Phase 3 was 8 times more effective than the 0.05% cyclosporine / 0.625% castor oil or 0.1% cyclosporine / 1.25% castor oil castor oil formulations in Phase 2. A scientifically sound comparison of the data showed no such increase in efficacy.

c. Dr. Schiffman used a "ratio of ratios" data analysis technique that exaggerated the differences in test results.

168. Third, the method that Dr. Schiffman used to calculate the differences in efficacy between the formulations overstated the differences between them.

169. Dr. Schiffman's statement that the Restasis formulation tested in Phase 3 led to an "8-fold improvement" over the 0.05% cyclosporin / 0.625% castor oil formulation tested in Phase 2 was based on a "ratio-of-ratios" calculation: Dr. Schiffman first compared patients' median change from baseline in corneal staining scores at week 12 for the 0.05% and 0.1% cyclosporin formulations in the Phase 2 study. He calculated that the change from baseline for

the 0.05 formulation was approximately one-quarter as large as the change from baseline for the 0.1% formulation. He then conducted a similar comparison of the 0.05% and 0.1% formulations in Phase 2 with regard to the median change in Schirmer scores without anesthesia, again concluding that the change from baseline was approximately one-quarter as large for the 0.05% formulation as for the 0.1% formulation. He then performed the same calculation for corneal staining and Schirmer scores without anesthesia for each of the two Phase 3 studies. The median improvement in the corneal staining scores for both Phase 3 studies was roughly the same, as was the median improvement in the Schirmer scores for the second Phase 3 study. However, Dr. Schiffman calculated the improvement in Schirmer scores for the first Phase 3 study as being approximately twice as great for the 0.05% formulation as for the 0.1% formulation.

170. As the *Allergan* court explained, Dr. Schiffman's calculations were "misleading" because it is based on a calculation *of the ratio of the differences* between the improvement from baseline for the 0.05% and 0.1% cyclosporin formulations for the two studies. Even though the actual difference in the median improvement in Schirmer scores for the 0.05% and 0.1% formulations in Phase 2 was only about 1.5 millimeters, the use of ratios to represent the difference suggested that the difference was 4:1 in favor of the 0.1% formulation. Similarly, although the difference between the 0.05% and 0.1% formulations in the first study of Phase 3 was not dramatic, depicting that difference as a ratio of the differences from baseline tended to exaggerate its significance by suggesting that the 0.05% formulation was twice as effective as the 0.1% formulation. Dr. Schiffman then calculated *the ratio of the two ratios* (2/.25), deriving a ratio of 8:1, which again exaggerated the difference between the 0.05% and 0.1% formulations as measured in the Phase 2 and Phase 3, suggesting that the 0.05% cyclosporin/1.25% castor oil

formulation performed eight times as well in the first study of Phase 3 as the 0.05% cyclosporin/0.625% castor oil formulation in the Phase 2 study.

171. The *Allergan* court provided a useful example that helps show why such a ratio-of-ratios calculation is misleading:

> Suppose that the baseline value on some metric was 10.00. Suppose further that the Phase 2 data showed an improvement to 10.01 for the 0.05% cyclosporine/0.625% castor oil formulation and an improvement to 10.03 for the 0.1% cyclosporine/1.25% castor oil formulation. Suppose further that the Phase 3 data showed an improvement to 10.01 for the 0.1% cyclosporine/1.25% castor oil formulation and an improvement to 10.03 for the 0.05%/1.25% castor oil cyclosporine formulation. Finally, suppose that statistical analysis showed that none of those small variations in performance were statistically significant, but were likely just the product of experimental noise. Nonetheless, the ratio of the measured improvements in the metric for the 0.1% cyclosporine/1.25% castor oil formulation to the 0.05% cyclosporine/0.625% castor oil formulation in Phase 2 would 3:1, and the ratio of the measured improvements in the metric for the 0.1% cyclosporine/1.25% castor oil formulation to the 0.05% cyclosporine/1.25% castor oil formulation in Phase 3 would be 1:3. The ratio of those two ratios would be 9:1. Any conclusion from the "ratio of ratios" that there was a nine-fold relative improvement in performance by the 0.05% formulation in Phase 3 over Phase 2 would obviously be spurious.[84]

172. Dr. Schiffman's calculations also ignored the fact that the Phase 2 study was quite small and that the difference in the raw numbers for the 0.05% cyclosporin formulation compared to the 0.1% formulation on some metrics, including Schirmer scores, were not statistically significant.

173. Furthermore, Dr. Schiffman selected only two categories of tests to compare the performance of the 0.05% and 0.1% cyclosporin formulations. In other test categories for the Phase 2 studies, the 0.05% formulation did better than the 0.1% formulation. As the Eastern

[84] *Id.* at 80-81.

District of Texas explained, "[i]n order to make an appropriate assessment of the Phase 2 study data, it is necessary to view that data globally, not to select the data points that are most favorable to a particular desired outcome."[85]

174. Thus, Dr. Schiffman again manipulated the raw data to create the illusion that 0.05% (Restasis) formulation was far more effective in the Phase 3 study than it was in the Phase 2 study. Put another way, Dr. Schiffman convinced the PTO that Allergan had achieved an unexpected result through a highly misleading interpretation of the data.

d. Dr. Schiffman concealed the fact that the data he relied on was over a decade old; prior art to the second wave patents.

175. Fourth and finally, Dr. Schiffman's declaration failed to inform the PTO that the data he relied on in his declaration had been published *thirteen years before* the second wave patent applications and *three years before* their priority dates. Thus, as the Eastern District of Texas noted, a "major flaw in Dr. Schiffman's presentation was [] that, *even if* the results reported in Sall would have been surprising at the time the Phase 3 trials were conducted, those results *were publicly known before the invention*."[86] In other words, the results published in the Sall paper were prior art to the second wave patents applications and could not serve as a basis for their patentability.

176. Had Allergan made clear to the PTO examiner that Dr. Schiffman's declaration was based on data lifted from prior art known to Allergan for over a decade, as Allergan's duty of disclosure, candor, and good faith required, the PTO examiner would have rejected all of the second wave applications for the same reasons it had denied every other prior application: the claims presented were obvious in light of the prior art.

[85] *Id.* at 81.

[86] *Id.* at 82 (emphasis added).

177. Based on these serious problems, the Allergan court would later conclude that Dr. Schiffman's "presentation to the PTO substantially overstated the difference between the clinical results obtained with the Ding formulations and the clinical results obtained with the Restasis formulation."[87] As the court explained:

> To the extent that Allergan relies on Dr. Schiffman's presentation to the PTO . . . and the fact that the examiner concluded that unexpected results had been shown . . . the Court finds that the presentation made to the examiner in 2013, including Dr. Schiffman's declaration and the accompanying exhibits, *painted a false picture* of the comparative results of the Phase 2 and Phase 3 trials. In addition, that presentation *created the misleading perception* that the evidence that Dr. Schiffman relied on to show unexpected results was not known at the time of the invention.[88]

178. The Allergan court would also later conclude that "the examiner's finding of unexpected results . . . was [based] on evidence that did *not accurately depict* the comparative results of the two Allergan studies and that was, in any event, disclosed in the prior art."[89] In other words, but for Allergan submission of Dr. Schiffman's highly misleading declaration, the PTO would never have issued the patent.

7. November 21, 2013: The Schiffman declaration convinces the PTO examiner to allow the second wave patents.

179. The Schiffman declaration had its intended effect. On November 21, 2013, the examiner reversed course and allowed the second wave patent claims. Trusting Dr. Schiffman and Allergan not to misrepresent the truth – as their duties of candor and good faith required –

[87] *Id.* at 133.

[88] *Id.* at 82.

[89] *Id.* at 82-83 (emphasis added).

the PTO examiner did not uncover the manipulations, false comparisons, and misrepresentations that the Schiffman declaration contained.

180. Instead, the examiner concluded that the Schiffman declaration,

> Is deemed sufficient to overcome the rejection . . . because: After carefully reviewing exhibits A-F, which compare the instantly claimed embodiment having 0.05%/1.25% castor oil with embodiments E and F of Ding et al. (0.10%/1.25% [cyclosporine/] castor oil and 0.05%/0.625% cyclosporine/castor oil ratios), Examiner is persuaded that, *unexpectedly, the claimed formulation (0.05% cyclosporine A/1.25% castor oil) demonstrated an 8-fold increase in relative efficacy* for the Schirmer Tear Test score in the first study of Phase 3 trials compared to the relative efficacy for the 0.05% by weight cyclosporine A/0.625% by weight castor oil formulation disclosed in Example 1E of Ding, tested in Phase 2 trials. . . .
>
> Exhibits E and F also illustrate that the claimed formulations comprising 0.05% cyclosporine A/1.25% castor oil also *demonstrated a 4-fold improvement in the relative efficacy* for the Schirmer Tear Test score for the second study of Phase 3 and *a 4-fold increase in relative efficacy* for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporine A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E).

181. Thus, the examiner allowed the second wave Restasis patents *based on* Dr. Schiffman declaration. He believed Allergan's representation that the Restasis formulation demonstrated 8- and 4-fold increases in efficacy over the 0.05% cyclosporine / 0.625% castor oil formulation tested in the Phase 2 trial.

182. But for this declaration, the examiner would not have issued the new Restasis patents. Indeed, during the trial of the second wave patents' validity, Dr. Schiffman conceded that his declaration was instrumental in persuading the PTO to grant the second wave applications.[90]

[90] *Allergan* at 40.

183. In January through April 2014, five of the applications issued as second wave patents, U.S. Patent Nos. 8,629,111 ("the '111 patent"), 8,633,162 ("the '162 patent"), 8,642,556 ("the '556 patent"), 8,648,048 ("the '048 patent"), and 8,685,930 ("the '930 patent"). (A sixth would issue in February 2016 as U.S. Patent No. 9,248,191 ("the '191 patent")).

184. In sum, Allergan procured the second wave patents through knowing, intentional fraud on the PTO.

C. Early 2014: Allergan wrongfully lists the second wave patents in the Orange Book.

185. Having acquired the second wave patents by fraud, Allergan then employed another tactic to frustrate the introduction of generic Restasis products – it listed the second wave patents the Orange Book.

186. Throughout the first quarter of 2014, Allergan listed every second patent in the Orange Book as soon as it issued. The dates of Allergan's listings of its second wave patents were:

Patent Number	Date of Orange Book listing
8,629,111 (the '111 patent)	January 14, 2014
8633,162 (the '162 patent)	January 22, 2014
8,642,556 (the '556 patent)	February 4, 2014
8,648,048 (the '048 patent)	February 11, 2014
8,685,930 (the '930 patent)	April 1, 2014

187. Each of these listings was wrongful.

188. Under the Hatch-Waxman Amendments, an NDA holder may only submit patent information to the FDA for listing in the Orange Book if the patent is one for which "a claim of

patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[91]

189. None of the second wave patents could "reasonably be asserted" against any applicants for generic Restasis. First, the second wave patents were knowingly acquired by fraud on the PTO; Allergan could not "reasonably" assert them against would-be generic makers. Second, in the context of litigation to enforce any one of the second wave patents, no reasonable brand company would realistically expect to prevail on the merits of the litigation; the obviousness of the patents would be revealed, as would the falsity of Allergan's assertions of surprising comparative efficacy of the 0.05% formulation as of the priority date of September 2003. As a result, Allergan could not "reasonably" assert them against a would-be generic competitor, as it harbored no realistic ability to prevail on the merits.

190. Allergan knew that the second wave patents were not eligible for listing in the Orange Book. It knew of its fraud. And it knew the patents would be declared invalid as obvious given the absence of any true, surprising efficacy of the 0.05% formulation as of the priority date of September 2003.

191. By listing the second wave patents in the Orange Book, Allergan imposed additional regulatory requirements on existing and future Restasis ANDA applicants as well as created the potential for regulatory exclusivities that should not have existed.

192. First, all generic manufacturers that had submitted their ANDA applications before the second wave patents issued were now required to amend their ANDAs to include certifications with respect to the '111 patent (and, sequentially, the other second wave patents). ANDA applicants already on file had likely made Paragraph III certifications with respect to the

[91] Sections 505(b)(1) and (c)(2) of the Act.

to the Ding I patent, i.e., the applicants would wait until after expiration of the Ding I patent in May 2014 to market their products. But after Allergan listed the second wave patents, the ANDA applicants were required to amend their ANDAs, either by (i) filing further Paragraph III certifications (and thus waiting *many years* for FDA approval), or (ii) filing Paragraph IV certifications to challenge those patents (thereby triggering Allergan's ability to bring immediate infringement litigation against them).

193. Second, by listing the second wave patents in the Orange Book, Allergan created the space for it to argue, and the FDA to accept, that a 30-month stay of approval for generic cyclosporine ophthalmic emulsion existed until at least 2018. Indeed, Allergan has taken this position in filings with the FDA and in filings with the *Allergan* court.

194. Third, by causing the second wave patents to be listed in the Orange Book, Allergan created the potential for one or more ANDA filers to argue that their Paragraph IV certification(s) to one or more of the second wave patents created a first-to-file exclusivity under which no other ANDA applicant could gain FDA approval for generic Restasis until 180 days after the first-to-file applicant had been on the market. (At least two ANDA applicants, and Allergan itself, would later make this argument to the FDA).

195. Allergan knew when it listed the second wave patents in the Orange Book that those listing would impose unwarranted regulatory hurdles to ANDA approval, would likely allow Allergan to bring immediate suit against ANDA applicants, and would create the potential for unwarranted 180-day exclusivities. The purpose and effect of Allergan's second wave patent listings was to hinder and impede competition in the market cyclosporine ophthalmic emulsion, 0.05%.

D. Early 2014: About five ANDAs for generic Restasis had been submitted to the FDA.

196. Beginning in 2011, generic pharmaceutical manufacturers – including some of the biggest brand and generic pharmaceutical companies in the world –submitted ANDAs seeking FDA approval to market cyclosporine ophthalmic emulsion, 0.05%.

197. The manufacturers known to have filed ANDAs with the FDA seeking approval to market cyclosporine ophthalmic emulsion, 0.05% *by early 2014* are listed below.

ANDA Applicant	ANDA No.	When ANDA First Submitted (If Known)
Watson	203463	November 14, 2011
Teva	203880	Probably 2011, because of first three digits (203)
Akorn	204561	2012
Mylan	205894	
Innopharma (Pfizer subsidiary)	206835	January 13, 2014

198. By the summer of 2015, the FDA had concluded that several of those ANDAs were substantially complete at the time they were first filed.

199. For example, the generic manufacturer InnoPharma (a Pfizer company) has revealed that in mid-2015, the FDA deemed its ANDA for cyclosporine ophthalmic emulsion, 0.05% to be substantially complete as of its original filing date, January 13, 2014.

200. To be deemed substantially complete, an ANDA must contain sufficient data that could plausibly support an FDA determination that the generic product is bioequivalent to the corresponding brand product, including drug release-rate data. The FDA's determination that InnoPharma's ANDA was substantially complete when filed on January 13, 2014 means that

InnoPharma's ANDA was sufficiently complete on that date such that the FDA could have made an approval determination.

201. Another example the comes from the generic manufacturer, Akorn. Akorn appears to have filed an ANDA in 2012 that the FDA subsequently determined (in mid-2005) to have been substantially complete at the time it was filed. Akorn has revealed that the FDA acknowledged its ANDA on June 30, 2015, and the acknowledgment appears to relate back to Akorn's original ANDA filing in 2012. (During a March 22, 2016 earnings call, Akorn CEO Raj Rai indicated that Akorn had submitted its ANDA for Restasis in 2012.[92] In fact, Akorn has stated, in public correspondence with the FDA, that its work in demonstrating to FDA the bioequivalence of its cyclosporine ophthalmic emulsion, 0.05% to Restasis formed the basis of FDA's June 2013 bioequivalence recommendations for Restasis).

202. In public correspondence with FDA, Apotex (another ANDA filer) stated that it interpreted FDA's "Dear Applicant" letter to all Restasis ANDA filers to necessarily imply that, by January 14, 2014, one or more ANDAs for cyclosporine ophthalmic emulsion, 0.05% had been submitted and deemed substantially complete.

203. Allergan itself has stated, in its public correspondence with FDA, that it "understands" that "on or about July 9, 2015, FDA purportedly 'received' at least five ANDAs for review," and that "the ANDAs were substantially complete . . . long ago." In that same public correspondence with FDA, Allergan stated that one of the ANDAs was submitted to FDA in 2013, and one was submitted as early as March of 2012. Therefore, even Allergan necessarily agrees, given FDA's definition of substantial completeness for an ANDA, that several ANDA

[92] Akorn Q4 2016 Earnings Summary Transcript, https://seekingalpha.com/article/3960291-akorns-akrx-ceo-raj-rai-business-update-2016-guidance-conference-call-transcript.

filers had sufficient data that could plausibly support FDA approval, including on the criterion of bioequivalence, as of early 2014.

E. January 2014: Allergan begins a series of abusive, sham petitions to the FDA.

204. Another prong of Allergan's multi-faceted scheme was to delay the FDA's approval of any Restasis ANDA by filing sham, repetitive petitions to the FDA. With the Ding I patent set to expire in May 2014, Allergan began to file in January 2014 what would become a series of petitions to the FDA attacking the FDA's articulated scientific basis for approving generic Restasis applications.

205. Allergan knew that its comments to the draft guidance would not necessarily delay generic entry – the FDA is only required to consider these comments, but is not required (as it is with a citizen petition) to formally respond to individual requests to take (or refrain from taking) action.

206. In January 2014 – and despite having already aired its criticism of the FDA's draft guidance during the August 2013 comment period – Allergan nonetheless began inundating the FDA with submission after submission challenging the FDA's approach to determining the requirements for approving applications for generic cyclosporine ophthalmic emulsion products.[93]

207. While Allergan claims that its citizen petitions were submitted to tell the FDA that "rushing prematurely to approve a proposed generic drug [not supported by *in vivo* clinical endpoint studies] poses a risk to patient health," Allergan's true goal was to delay the FDA's

[93] *See* Allergan, Inc., Citizen Petition, Jan. 15, 2014, FDA-2014-P-0117 ("January 2014 Citizen Petition"); Allergan, Inc., Citizen Petition, Feb. 28, 2014, FDA-2014-P-0304 ("February 2014 Citizen Petition"); Allergan Inc., Citizen Petition, Dec. 23, 2014, FDA-2015-P-0065 ("December 2014 Citizen Petition"); Allergan, Citizen Petition, Aug. 4, 2017, FDA-2017-P-4745 ("August 2017 Citizen Petition").

review of any Restasis ANDA. Saddling the agency with baseless, duplicative citizen petitions relating to the 2013 draft guidance was a tactic that Allergan told investors exemplified its response to "intense competition from generic drug manufacturers."[94]

208. On January 15, 2014, Allergan filed the first petition.

209. On February 28, 2014, it filed another petition, repeating the demands and arguments of the earlier one, but adding a required certification that acknowledged Allergan was aware of the existence of at least one specific instance of a generic company seeking to gain approval for a cyclosporine ophthalmic emulsion, 0.05% product (the "February 2014 petition"). (Allergan later withdrew the earlier January petition, effectively allowing the February petition to replace it).

210. The February 2014 petition largely parroted Allergan's August 2013 comments to the FDA's June 2013 guidance. The petition challenged the FDA's decision to allow for *in vitro* studies to establish bioequivalence for cyclosporine emulsion ophthalmic drug products. It made six demands of the FDA, including that it "[w]ithdraw the Draft Cyclosporine BE Guidance and make clear that the only way to demonstrate bioequivalence to Restasis is through comparative clinical endpoint studies," that it "[n]ot accept for filing, but instead reject as incomplete, any ANDA referencing Restasis that does not include data derived from a comparative clinical endpoint study," and that it "[m]ake clear that FDA will not approve any ANDA referencing Restasis based exclusively on in vitro assays until there is sufficient evidence from clinical studies that those assays correlate to in vivo bioavailability in humans."

[94] February 2014 Citizen Petition at 2; Allergan, Inc., SEC Form 10-K for FY Ended 12-31-2014 at 12, 48.

211. The February 2014 petition cited to the public comments submitted by its cadre of paid doctors, ostensibly "draw[ing] from their clinical experience, criticizing the draft guidance's in vitro approach."

212. Allergan ostensibly supplemented the petition on May 29, 2014 and then submitted it again on October 31, 2014.

F. November 2014: The FDA rejects the first of Allergan's sham petitions.

213. On November 20, 2014 – only months after Allergan had filed the February petition and only weeks after its most recent, ostensible supplement – the FDA denied all of the substantive demands made by Allergan.

214. The FDA provided a thorough explanation of the scientific determination on which the draft guidance was based.

215. *Scientific Rationale for In Vitro Option*. The purpose of a bioequivalence study is to determine whether any formulation differences between a proposed generic product and the reference listed drug cause the active ingredient to reach the site of action at a different rate or to a different extent. There are two key concerns when determining bioequivalence of a locally acting topical ophthalmic product: (i) are the test and reference products formulated similarly such that the release characteristics are the same between the two products, and (ii) will the amount of drug uptake by the ocular tissues be the same, or will absorption be affected by differences in formulation and/or manufacturing of the two products?

216. The FDA considers comparative clinical endpoint studies to be relatively insensitive at detecting the manufacturing and formulation variables, which have the greatest

potential to affect the bioavailability of topical ophthalmic products.[95] In particular, *in vivo* clinical endpoint studies, which measure formulation differences indirectly rather than directly, may be limited by confounding variables such as different severities of disease and variability in the definition of the instrument used to measure efficacy, among other issues.

217. As a result, in recent years, the FDA researched alternative, *in vitro* bioequivalence testing methods that can be expected to detect a meaningful difference between the generic and listed versions of non-systemically absorbed drugs in safety and therapeutic effect.[96] And it has explored many different approaches to demonstrating bioequivalence for locally acting, non-systemically absorbed topical drug products, including generic products that are quantitatively and qualitatively the same as the reference listed drug.

218. When a generic product is quantitatively and qualitatively the same as the reference listed drug, the *only* differences it could have from the reference listed drug would be in its physicochemical properties. Such differences can arise only from differences in the generic product's manufacturing process and formulation steps, and can affect the generic product's drug release, absorption, and dose uniformity. When a generic product's physicochemical properties and drug release rate are similar to those of the reference listed drug, bioavailability is expected to be the same for both products.

219. In recent years, based upon its research findings and other available information, the FDA has recommended *in vitro* studies for demonstrating the bioequivalence of several locally acting products when the formulations of the products are the same, including for

[95] 21 C.F.R. § 320.24(b)(4) (stating that comparative clinical endpoint trials are "the least accurate, sensitive and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence").

[96] *See* section 505(j)(8)(C) of the FDCA.

cyclosporine ophthalmic emulsion.[97] As such, the 2013 draft cyclosporine guidance includes a recommended *in vitro* option for proposed product formulations that are quantitatively and qualitatively the same as the reference listed drug and that also meet other specified criteria.

220. In considering the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, the FDA has also reviewed the option of conducting a comparative clinical endpoint study to demonstrate bioequivalence of cyclosporine ophthalmic emulsion. It concluded that a comparative clinical endpoint study likely *would not be as reliable* at detecting differences in the formulation and manufacturing process of a proposed generic product when the reference listed drug shows only a modest clinical effect.

221. The FDA also concluded that such trials might present economic and logistical challenges for ANDA sponsors. Nevertheless, the 2013 draft cyclosporine guidance provides an *in vivo* clinical endpoint option, and it recommends that a sponsor proposing to conduct such a trial first consult with the FDA by submitting the study protocol.

222. Based on these considerations, the FDA determined that, for cyclosporine ophthalmic emulsion, an *in vitro* study is likely more sensitive, accurate, and reproducible than a comparative clinical endpoint study to establish bioequivalence, which is why the 2013 draft guidance includes an *in vitro* testing-only option.

223. *Comparing formulations that are quantitatively and qualitatively the same.* The FDA's recommended *in vitro* option for cyclosporine ophthalmic emulsion first provides that the proposed generic product formulation be quantitatively and qualitatively the same as the

[97] For example, the FDA recommended demonstrating bioequivalence via in vitro methods for locally acting oral dosage form drug products with Ql/Q2 formulations (e.g., vancomycin capsules), for a locally acting topical dermatological product with Ql/Q2 formulation (i.e., acyclovir ointment), and for a locally acting inhalation suspension with Ql/Q2 formulation (i.e., budesonide inhalation suspension).

reference listed drug (*i.e.*, Restasis) because formulation differences (such as differences in the inactive ingredient) may alter cyclosporine bioavailability. The *in vitro* option is available *only* when it is confirmed that the identity and amount of each component in the proposed generic drug product is the same as that contained in the reference listed drug. For a proposed generic product that is not quantitatively and qualitatively the same as the reference listed drug, the *in vivo* study with a clinical endpoint would be the recommended option.

224. *Acceptable Comparative Physiochemical Characterization (Q3).* Of course, the FDA recognizes that even a proposed generic product that is quantitatively and qualitatively the same as the reference listed drug can have clinically significantly differences in its physiochemical profile owing to differences in how the generic product was manufactured and formulated. Accordingly, the 2013 draft guidance recommends that an ANDA applicant seeking to establish bioequivalence solely through in vitro studies demonstrate that the proposed generic product has a physiochemical profile acceptably similar to that of the reference listed drug. It recommends that applicants perform comparative physiochemical characterization of globule size distribution, viscosity, pH, zeta potential, osmolality, and surface tension.

225. *Acceptable comparative in vitro release rates*. The *in vitro* option also recommends that an ANDA applicant confirm that the release rate of cyclosporine from its proposed generic product is comparable to that of the reference listed drug. An in vitro release rate reflects the combined effect of several physical and chemical properties in both the drug substance and the drug product. Manufacturing methods and processes (e.g., heating, mixing, or cooling) may change the formulation attribute, thereby affecting the rate of drug release and the drug's bioavailability. Confirmation that a proposed generic product has a comparable release rate to that of the reference listed drug can help ensure that the proposed generic product will

deliver cyclosporine to the ocular tissues for absorption in a manner comparable to that of the reference listed drug.

226. In sum, the FDA determined that a proposed cyclosporine ophthalmic emulsion formulation that meets the three recommended criteria – quantitative and qualitative sameness, physiochemical sameness, and an acceptable comparative *in vitro* release rate – should become available at the site of action at a rate and to an extent that is not significantly different from that of the reference listed drug, thus meeting the requirement for demonstrating bioequivalence.[98] Whether the data and information in a particular ANDA are sufficient to demonstrate bioequivalence is an issue the FDA determines during review of a specific proposed ANDA.

227. The FDA rejected each of the positions asserted by Allergan in its February 2014 petition as to the science and the law.

228. As to the science, the FDA noted the exacting requirements of the 2013 draft guidance *in vitro* option, viz., that an "*in vitro* option is available *only* when it is confirmed that the identity and amount of each component in the proposed generic drug product is the same as that contained in the reference listed drug. For a proposed generic product that is not quantitatively and qualitatively the same as the reference listed drug, the *in vivo* study with a clinical endpoint would be the recommended option." Recognizing that even those products that are the same for quantitatively and qualitatively can, through formulation or manufacturing differences, have different bioavailability, the in vitro option also requires an ANDA applicant seeking to "demonstrate that the proposed generic product has a physiochemical profile acceptably similar to that of the [reference listed drug] . . . [by comparative] . . . physiochemical

[98] *See* 21 CFR § 320.l(e).

characterization to assure that . . . generic formulations can be expected to deliver the same amount of drug for absorption at the site of application as the [reference listed drug] . . . [through measuring the seven characteristics of] . . . globule size distribution, viscosity, pH, zeta potential, osmolality, and surface tension."

229. The FDA observed that it was "confident" the *in vitro* option had "general scientific validity" under any reasonable standard of that concept. Its guidance was "substantiated by scientific evidence" including peer-reviewed research conducted by the FDA Office of Testing and Research. Criticisms of that study by Allergan "were simply outside the scope" of that publication. The FDA observed that Allergan "offer[ed] no evidence" to contradict the FDA's position that measurement of the physiochemical properties identified by the guidance were insufficient to measure bioavailability on the basis of current science. The FDA also rejected Allergan's claim that current methods of testing were inadequate to the task. It rejected Allergan's claim that the testing methods inadequately assessed safety and efficacy, seeing "no merit to this argument." It rejected Allegan's confusion in trying to use the rejection of in vitro data when applied to unfounded comparative marketing claims to the determination of bioavailability under the stringent conditions required by the guidance. It found suspicious Allergan's claim that data generated during the Restasis NDA satisfied the guidance criteria, such that Allergan's claim that data showed the guidance to be insufficient was not credible. And it rejected Allergan's attack on the requirement for release rate testing, noting that the guidance recommends that "'[a]cceptable comparative in vitro drug release rate tests' be performed on the reference listed drug and test formulation, and the burden is on ANDA applicants to develop a suitable *in vitro* method for measuring drug release, not on FDA to prescribe one."

230. Finally, as to the science, the FDA noted that the alternative to *in vitro* testing – *in vivo* – was inferior. It stated,

> Because comparative clinical endpoint studies measure formulation differences indirectly rather than directly, it is more likely that in vivo testing will result in erroneous determinations of bioequivalence than in vitro testing. Thus, we believe that the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence likely will be in vitro testing, as recommended in the Draft Cyclosporine BE Guidance. Moreover, given the modest clinical benefit shown for cyclosporine ophthalmic emulsion, such a comparative clinical endpoint study could require more than 2,000 subjects with dry eye disease to pass the statistical tests for bioequivalence. Consequently, we recognize that a comparative clinical endpoint study may pose economic and logistical feasibility concerns.

231. As to Allergan's arguments on the law, the FDA concluded that "[n]one of your legal conclusions has merit . . . ."

232. The FDA summed up, stating that the in vitro-only option in its June 2013 draft guidance was consistent with "the Agency's authority to make bioequivalence determinations on a case-by-case basis using in vivo, in vitro, or both types of data," which enabled the FDA "to effectuate several long-standing policies that protect the public health" when approving ANDAs for generic drugs." Those policies included "(1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards for approval; (2) permitting the Agency to use the latest scientific advances in approving drug products; (3) protecting the public by ensuring only safe effective generic drugs are approved for marketing; and (4) making more safe and effective generic drugs available."

233. The FDA thus rejected every substantive demand, and each factual and legal argument, Allergan posed in its February 2014 petition. The only demands that it "allowed" (in quotations given the pyrrhic nature of the grant) were (i) an opportunity to comment on the

guidance (which, of course, Allergan had already been given), and (ii) an articulation of the basis for FDA's guidance decision (which it had already done, and was required to do in response to any petition on the subject, regardless how frivolous the demand might be).

234. After the FDA issued its November 20, 2014 rejection of Allergan's petition, Allergan did not appeal that decision. Appealing the decision in the courts might eventually resolve the issues (likely against Allergan), but that would not hinder the FDA's ordinary course review of then-pending ANDAs for generic Restasis products.

G. December 2014: Allergan files a further abusive, sham petition to the FDA.

235. On December 23, 2014 – only four weeks later – Allergan filed yet another petition with the FDA (the "December 2014 petition").

236. The December 2014 petition consisted largely of repeating the positions asserted the February one. The December 2014 petition again demanded that the FDA require Restasis ANDA filers to conduct in vivo testing only.

237. Allergan supplemented the December 2014 petition four times, including an August 16, 2015 supplement in which Allergan demanded (among other things) that the FDA convene a committee of outside experts to evaluate the use of in vitro methods for generic Restasis, and that the FDA refuse to receive, review or approve any Restasis ANDAs until that outside committee's evaluation was complete.

238. At the time that Allergan filed the December 2014, no reasonable company would have a realistic expectation that the FDA would adopt any of the substantive demands made in the petition. The FDA had already addressed, and rejected, most of the arguments it made. The December petition, and its supplements, provided no new, reliable clinically relevant information upon which it could allow, consistent with its statutory mandate to make decisions based on the science and the law, its regulatory positions.

H. August 2015: Allergan begins a series of abusive, sham patent litigations.

239. In response to Allergan's Orange Book listings, and exactly as Allergan had planned, generic competitors had submitted to the FDA original or amended paragraph IV certifications with respect to the second wave patents.

240. On or about June 2015, the FDA issued a series of acknowledgements of the receipt of at least several ANDAs for cyclosporine emulsion 0.05%. Having received those acknowledgements, several generic manufacturers (Apotex, Akorn, Mylan, and Teva) all served paragraph IV certifications on Allergan within weeks of each other starting in July 2015. The paragraph IV certifications asserted that the second wave patents either were invalid or non-infringed. Several other ANDA filers would later follow suit. The following is a summary:

Applicant	ANDA number	Date second wave Paragraph IV certification served
Watson	203463	January 2014
Teva	203880	July 23, 2015
Akorn	204561	July 13, 2015
Mylan	205894	July 20, 2015
Innopharma (Pfizer subsidiary)	206835	August 3, 2015
Apotex	207606	July 23, 2015
Famy Care	208469	January 29, 2016
TWi Pharmaceuticals	209064	June 8, 2016
Deva Holding	209811	November 11, 2016

241. In August of 2015 – and having received these paragraph IV certifications necessitated by Allergan's Orange book listings – Allergan filed suit against Akorn, Teva, Apotex and Mylan alleging infringement of various claims in the first five of the six second

wave patents

242. Over time and as additional generic makers served notice of their ANDAs and paragraph IV certifications on Allergan, Allergan filed additional suits against its would-be competitors. All these suits (the "*Second Wave litigation*") were filed on the following dates:

Defendant	**PIV Notice Received**	**Complaint Filed**	**Patents**
Actavis[99]	01/21/14	03/06/14	'111
Teva	07/23/15	08/25/15	'111, '162, '556, '048, '930
Apotex	07/24/15	08/25/15	'111, '162, '556, '048, '930
Akorn	07/13/15	08/25/15	'111, '162, '556, '048, '930
Mylan	07/21/15	08/25/15	'111, '162, '556, '048, '930
InnoPharma	08/03/15	09/08/15	'111, '162, '556, '048, '930
Famy Care	03/01/16	04/12/16	'111, '162, '556, '048, '930, '191
TWI	06/09/16	07/21/16	'111, '162, '556, '048, '930, '191
Deva Holdings	11/11/16	12/22/16	'111, '162, '556, '048, '930, '191

243. No reasonable brand company would have a realistic expectation of prevailing on the merits of the *Second Wave litigation*.

244. Federal court patent litigation affords parties the opportunity to discover facts, conduct orderly construction of the applicable patent claims, reveal actual facts that stubbornly lurk behind broad misstatements of statistical fact, compare the actual timing of claimed inventiveness as compared to the true priority date, and deliberately determine the actual merits of validity and infringement of patents.

[99] These allegations do not rely on the nature of the claims against Watson/Actavis.

245. In the stark light of federal patent litigation, no reasonable company in the position of Allergan would have a realistic expectation of avoiding a court final ruling that the second wave patents were invalid for obviousness over the prior art as of the priority date of September 2003.

246. First, the second wave patents were prima facie obvious over the Ding I patent and the Sall and Stevenson publications. Allergan itself had conceded this in unequivocal terms during PTO prosecution.

247. Second, Allergan was cornered into having to take the position that, as of the priority date of September 2003, it had uncovered some unexpected and surprising attributes to the 0.05% formulation as compared to the 0.1% one. But the data that Allergan used to reach that ostensible conclusion dated back to its own studies in 2000 – studies that had been publicly reported *years earlier* than the priority date.

248. Third, any reasonable litigant would not expect a federal court to accept the machinations to which Allergan's declarants were required to go – rejecting the express conclusions of Allergan's prior publications, deleting statistical significance data, comparing data between two studies conducted under materially different conditions, misleadingly presenting conclusions in the form of inflated ratios (and ratios-on-ratios), ignoring scores of data points in favor of a few outliers, ignoring that the source of the purported invention had been publicly reported years earlier.

249. Fourth, the second wave patents had been procured by fraud. Allergan knew this. Its enforcement of them was a sham.

250. Finally, while not dispositive of the sham nature of the *Second Wave litigation*, the results of that litigation show the plausibility of the allegations that there was no realistic

expectation of a win by Allergan on the ultimate merits.

I. February 2016: The FDA rejects Allergan's second petition to the FDA.

251. On February 10, 2016, the FDA denied all of the substantive demands made by Allergan in its December 2014 petition and various supplements to it. In doing so, the FDA rejected each of the positions asserted by Allergan on the science and the law.

252. The FDA first noted that the December 2014 petition "repeats many of the assertions that were at the center of Allergan's previous petition." Those assertions, the FDA found, were largely not even worth a further response by the Agency.

253. The FDA also observed that much of Allergan's complaints treated the draft guidance in a conceptually inaccurate way – Allergan was treating a draft guidance as a final, immovable position. But as the FDA pointed out, the document clearly "informs the reader via a conspicuously placed text box" that the "draft guidance, *once finalized*, will represent the Food and Drug Administration's (FDA's current thinking on this topic." Since the draft guidance "is a living, science-based document that is subject to change as new data and information on cyclosporine ophthalmic emulsion become available," Allergan's treatment of it as a static FDA position was not correct. (Indeed, on the same day that the FDA denied the petition, the FDA issued modifications to the in vitro recommendations in the draft guidance to refine several requirements in the physiochemical characterization and statistical analysis).

254. The FDA also rejected, once again, Allergan's rehashed arguments about the ostensible need for showing an established in vitro-in vivo correlation (IVIVC). And the FDA rejected Allegan's citation to FDA-funded research on topical ophthalmic suspensions and emulsions as having "no bearing on the scientific validity" of the draft guidance; among other things, that research did not even involve cyclosporine ophthalmic emulsion. It rejected

Allergan's citation to a statement attributed to a USP Expert Panel; since that panel "did not support [the] statement with evidence . . ." there was no reason for FDA to credit it.

255. The FDA also, once again, rejected Allergan's attack that *in vitro* testing of physiochemical properties of emulsions that are quantitatively and qualitatively the same was invalid for determining bioequivalence. It found "misleading" Allergan's characterizations of comments made at an April 2015 public meeting. Because Allergan had repeated arguments about its NDA emulsion tests, the FDA reexamined that data; the FDA wrote it "still find[s] that none of Allergan's test emulsions [were] comparable to Restasis" such that arguments about their lack of bioequivalence were unhelpful. Indeed, Allergan's presentation of some of that data was "misleading." And Allergan had not even tried to determine if those emulsion examples had comparative release rates – standing on its theoretical argument that the FDA prescribe such a test rather than have the party claiming bioequivalence to show one. In short, Allergan, as the FDA put it, "did not follow" the draft guidance it attacked; yet Allergan argued that use of that guidance could not yield bioequivalent results. And as the FDA put it, "Allergan's claim to the contrary confuses a scientific obstacle (which FDA expects applicants to overcome to support approval) for a scientific impossibility . . . ."

256. The FDA's February 2016 rejection so further flaws with the Allergan petition. The FDA was "unable to respond" to Allergan's assertion that the FDA had not acknowledged "other directly relevant data" because "Allergan did not specify the other data that it contends we ignored." Allergan's presentation of globule size distributions used neither instrumentation nor a methodology "appropriate for the pivotal comparisons" envisioned by the guidance; indeed, Allegan did not even use the same methodology when measuring the test batches than that used to measure the reference product – a fatal,

scientific flaw. Allergan's citation to the FDA's recommendations for *in vivo*-only bioequivalence testing for solution or suspension products had no relevance to cyclosporine emulsion; the FDA's "bioequivalence recommendations are determined on a case-by-case basis depending on the drug under study," not for groups of different products with different characteristics. Allergan "exaggerated" the significance of the FDA's extensive comments for in vivo testing of some other topical ophthalmic products; as the FDA put it, "the degree of thought that FDA put into developing these guidances cannot be divined" from the number of comments the FDA provides.

257. The FDA concluded it "has clear legal authority to receive and approve an ANDA for cyclosporine ophthalmic emulsion that relies exclusively on in vitro testing data." As a result the FDA, once again, rejected all of Allergan's substantive demands. The FDA did agree (i) to disclose (as it had already done) the *in vitro* bioequivalence methods it intended to accept for ANDAs that refer to Restasis, and (ii) to respond specifically to the Allergan's testing of nine experimental test emulsions (and in doing so rejected them as scientifically unreliable).

258. After the FDA issued its February 2016 rejection of Allergan's December 2014 petition, Allergan did not appeal that decision. Appealing the decision in the courts might eventually resolve the issues (likely against Allergan), but that would not hinder the FDA's ordinary course review of then-pending ANDAs for generic Restasis products.

259. In 2016, the FDA issued further details to its draft guidance for cyclosporine ophthalmic emulsion products. Allergan commented on those amendments.

J. August 2016: Allergan files a third petition to the FDA.

260. On August 4, 2016, Allergan filed yet another petition with the FDA, once again attacking the FDA's articulated scientific basis for approving generic Restasis. This petition

predictably requested – again – that the FDA refuse to accept or approve any pending ANDAs unless supported by in vivo clinical endpoint studies.[100] Allergan supplemented this petition on October 13, 2017.[101]

261. At the time that Allergan filed the August 2016 petition, no reasonable company would have a realistic expectation that the FDA would adopt any of the substantive demands made in the petition. The FDA had already addressed, and rejected, most of the arguments it made. The August 2016 petition, and its supplement, provided no new, reliable clinically relevant information upon which it could allow, consistent with its statutory mandate to make decisions based on the science and the law, its regulatory positions.

K. September 2017: Allergan enters an anticompetitive agreement with the Saint Regis Mohawk Tribe to avoid invalidation of the second wave patents.

262. Allergan's latest effort to forestall competition in the market for cyclosporine stems from a series of *inter partes* review requests.

263. In June 2015, Apotex had petitioned the PTO board to initiate an *inter partes* review of the second wave patents (Apotex subsequently provided notice of its paragraph IV certifications to Allergan on July 23, 2015).

264. Allergan settled the Apotex *inter partes* proceedings in December 2015, on undisclosed terms, just days before the board was set to rule on the likelihood that the Board would invalidate the second wave patents. By then however, other ANDA applicants, including Mylan and Teva, had also petitioned the board for *inter partes* proceedings on the second wave patents.

[100] August 2017 Citizen Petition at 1.

[101] Supplement to Allergan's August 4, 2017 Citizen Petition, Docket No. FDA-2017-P-4745 (Oct. 13, 2017) ("October 2017 Supplement").

265. In December 2016, the board resolved the same question that the Allergan settlement with Apotex mooted the year before, concluding there was a reasonable likelihood that each of the second wave patents would be invalidated upon the Board's further review. That conclusion triggered subsequent proceedings against all six of the second wave patents.[102]

266. On September 8, 2017, Allergan entered into an ostensible agreement with Mohawk to convey ownership of the second wave patents to Mohawk with an exclusive license back to Allergan for "all FDA-approved uses in the United States." The agreement also included a promise by Mohawk that it would not waive its sovereign immunity with respect to any IPR or other administrative action in the PTO related to the second wave patents. The agreement further provided for a payment to Mohawk of $13.75 million from Allergan, plus potentially $15 million in annual royalties. On September 22, 2017, after Mohawk and Allergan agreed to this unlawful transfer of property rights, Allergan, using Mohawk as a conduit, petitioned the PTAB to dismiss the remaining pending IPRs for lack of jurisdiction based on tribal sovereign immunity.

267. No objectively reasonable litigant could expect these obstructionist tactics to succeed. Multiple cases have rejected similar schemes to game the law, including in the context of sovereign tribes where the only interest Mohawk had was in being paid for the cover of immunity.[103]

268. The *Allergan* court allowed Mohawk to be joined as a co-Plaintiff, but only to ensure that any judgment it rendered would apply to Mohawk. The court explained that despite

[102] Because the terms of Allergan's settlement with Apotex in December 2015 (that avoided for as much as a year any risk that any of the second wave patents would be invalidated) were not made public, Plaintiffs s are presently unable to determine the extent to which that settlement may have violated *FTC v. Actavis*, 570 U.S. 136 (2013), and thus constitute yet another component in Allergan's overall scheme.

[103] *See People ex rel. Owen v. Miami Nation Enterprises*, 386 P.3d 357 (Cal. 2016).

its "serious concerns about the legitimacy of the tactic that Allergan and Mohawk have employed," it would "adopt the safer course of joining Mohawk as a co-Plaintiff, while leaving the question of the validity of the assignment to be decided in the *inter partes* proceedings, where it is directly presented."[104]

269. Allergan has made no secret of its subjective bad faith in seeking to add Mohawk as a defendant in the *inter partes* reviews. Allergan's chief executive, Brent Saunders, explicitly acknowledged that Allergan pursued the deal with Mohawk not to advance competition on the merits, but rather to avoid "double jeopardy"; that is, to intentionally disrupt adjudicative proceedings in one of the two venues, even though Allergan itself had initiated proceedings in the other and could voluntarily dismiss that other action at any time.

270. Mohawk, for its part, entered the agreement for the money. Mohawk is not entering the pharmaceutical industry. In fact, Mohawk has publicly disclaimed any actual business interest in the pharmaceutical industry.[105] Licensing the second wave patents back to Allergan was not a natural outgrowth of any ownership interest Mohawk had prior to September 2017. And, from Mohawk's comments, the agreement was not made pursuant to a natural future interest either. In entering this contract, Mohawk was not acting in its sovereign capacity, *e.g.*, regulating the sale or use of cyclosporine on a reservation.

L. October 2017: The Allergan court invalidates the second wave patents.

271. Following an August trial, on October 16, 2017, the Eastern District of Texas

[104] *Allergan* at 4, 9.

[105] *See* Saint Regis Mohawk Tribe Office of Technology, Research and Patents, Frequently Asked Questions About New Research and Technology (Patent) Business at 1, https://www.srmt-nsn.gov/_uploads/site_files/Office-of-Technology-Research-and-Patents-FAQ.pdf ("[T]he Tribe is not investing any money in this business. Its only role is to hold the patents, get assignments, and make sure that the patent status with the US Patent Office is kept up to date.").

(Federal Circuit Appellate Judge William C. Bryson, sitting by designation) held the second wave patents were invalid for obviousness. In the thorough opinion, the *Allergan* court found that Allergan had secured these patents by "paint[ing] a false picture" of the relevant data.[106] As the Court explained, Allergan had conceded in 2009 that the Restasis formulation would have been "readily envisage[d]" from the *Ding I* patent. And the data Allergan relied on to show unexpected results did not, in reality, demonstrate anything unexpected. In any event, this data was actually prior art and could not be relied on to prove the patentability of the second wave patents.

272. Despite the lack of any ultimate objective merit to its litigation, Allergan pressed its claims in the *Second Wave litigation* for years.

273. The objective merits were irrelevant, however, to Allergan's true purpose. Allergan filed suit not to vindicate any legitimate patent infringement issues, but to add to its efforts to frustrate the introduction of generic Restasis products. Its motives were financial – for a $1.5 billion/year franchise, every extra month Allergan could postpone competition from generic Restasis added another $125 million to its revenues.

M. January 2018: The FDA rejects Allergan's third petition.

274. On January 2, 2018, the FDA rejected Allergan's third petition.

275. Given the repetitive and unsupported nature of the issues this petition had once again posed, the FDA's rejection was brief. And once again, it reminded Allergan of the publicly stated requirements for approval of generic Restasis.

[106] *Allergan* at 82.

N. In the absence of Allergan's scheme to monopolize, generic Restasis would have been on the market by as early as May 2014.

276. Were it not for Allergan's execution of its unlawful scheme, generic cyclosporine ophthalmic emulsion, 0.05% would have been approved and on the market at an earlier period, beginning as early as May 2014.

277. ANDAs for generic cyclosporine ophthalmic emulsion 0.05% were submitted to the FDA many years ago, and in some cases over two years before the expiration of the Ding I patent in May of 2014. Given usual expectations for the timing to approval of ANDAs, the lengthy period following submission of ANDAs for generic Restasis fall well within those approval time periods.

278. Specifically, as to ANDAs for generic cyclosporine ophthalmic emulsion, 0.05%, the FDA in mid-2015 acknowledged the filing of several ANDAs. Those acknowledgements constitute a ruling that those ANDAs were substantially complete at the time that they were filed. This indicates that at the time of their submission – in some cases months or years before expiration of the Ding I patent – those applications contained sufficient information from which review and an approval decision could be made.

279. Some of the largest and most sophisticated and successful drug companies had submitted the ANDAs for generic cyclosporine ophthalmic emulsion, 0.05%. The active and inactive ingredients are commonly known, easily available and unprotected by patents. The actual production of generic cyclosporine ophthalmic emulsion, 0.05% poses little manufacturing or formulation obstacles. To be sure, each ANDA applicant had to meet the challenges posed by the FDA's in vitro testing requirements to establish bioequivalence of their product. But few actual production obstacles stood in the way to producing the product and readying for launch distribution.

280. The obstacles Allergan's scheme constructed – both to the ordinary course review and approval of ANDAs for generic cyclosporine ophthalmic emulsion, 0.05%, and to the ability of an ANDA applicant's willingness and ability to launch a product – are of a kind that normally do cause, and are expected to cause, delay of generic entry. Obtaining patents by fraud, and enforcing them, burdens ANDA applicants and delays generic entry. In the absence of the second wave patents, there would have been no patent obstacle to approval or launch of generic Restasis after May 2014. Listing patents unlawfully in the Orange Book creates the ability immediately to file litigation (upon receipt of notice of the paragraph IV certification), and to erect the potentials for a 30-month stay of FDA and/or a 180-day exclusivity where neither should exist. Filing petitions to the FDA that are unlikely to change FDA policy nevertheless disrupt the ordinary course of the FDA's review and approval of ANDAs. Despite the FDA's misgivings about the lack of sound, substantive bases for Allergan's citizen petitions, the FDA was nonetheless obligated to specifically respond to each of Allergan's requests. Allergan's rampant litigiousness, including sham transfer of patent right to avoid PTO scrutiny, signals to private would-be generic makers and the FDA that Allergan will stop at almost nothing to frustrate generic competition. Taken signally or in combination, these acts tend to delay competition.

281. Delay of generic approvals also follows from some FDA statements. For example, in the February 2016 rejection letter, the FDA informed Allergan that it would "not approve or receive any ANDA referencing Restasis based on in vitro assays unless and until FDA responds specifically to the findings of Allergan's testing of nine experimental test emulsions" submitted

with the December 2014 Citizen Petition.[107] While that letter itself had provided the response needed, the FDA effectively acknowledged that Allergan's petition – although based on faulty science and ultimately having no merit whatsoever – had already delayed it approving any Restasis ANDA.

282. An inference of delay also follows from Allergan's intent and its actions. Allergan's acts were intended to have the effect of delaying generic entry. They were not idly undertaken, nor undertaken to improve public health or safety. (Note, for example, Allergan's choice not to bring suit to challenge denial of its petitions). It is reasonable to infer Allergan's actions had their intended consequence.

283. Delay of generic cyclosporine ophthalmic emulsion, 0.05% is acknowledged by the generic industry itself. As Mylan's CEO Heather M. Bresch stated in Mylan's November 3, 2017 earnings call, "I think this is a great example of [Mylan] persevering through what I would call [Allergan's] pretty desperate legal maneuvers to try to maintain a monopoly that should have been gone a couple of years ago, and our ability continue to fight not only in the courts, but with the science and have a clear pathway to approvals."[108]

284. Had scientists, regulatory professionals, and lawyers at Mylan, other generic manufacturers, and the FDA not been tied up by Allergan's "desperate legal maneuvers," and had they not been forced for years to "continue to fight" Allergan's anticompetitive conduct,

[107] More specifically, Allergan submitted data regarding a series of emulsions that it claimed passed the agency's in vitro test but were nevertheless not bioequivalent to Restasis. FDA 2016 Denial at 24. The FDA pointed out that none of these emulsions in fact met the in vitro test, *id.* at 24-26 – a fact that Allergan itself partially admitted, *id.* at 25-26 & n.107 – but the agency nevertheless obligated itself to fully respond to the emulsion data before approving any Restasis ANDAs. *Id.* at 44.

[108] Mylan Q3 2017 Earnings Call Transcript, https://seekingalpha.com/article/4121235-mylan-nv-myl-q3-2017-results-earnings-call-transcript?all=true&find=%22and%20on%C2%A0RESTASIS%E2%80%A6.

they would have remained focused solely on ensuring that safe and effective generic version(s) of Restasis were approved "years ago" at, or as near as possible to, the expiration of the Ding Ipatent in May 2014. This delay in competition is a direct result of Allergan's anticompetitive scheme and the exact result that Allergan intended to achieve.

285. But for Allergan's misconduct, one or several of the ANDA filers would have received FDA approval and would have been able to supply the commercial quantities of generic Restasis necessary to meet market demand upon expiration of the Ding I patent as early as May 2014. Other ANDA applicants would have been ready at a later date but still earlier.

VI. CLASS ALLEGATIONS

286. Plaintiffs bring this action on behalf of themselves and, under Fed. R. Civ. P. 23(a), (b)(2), and (b)(3), as representatives of an End Payor Class defined as follows:

> All persons or entities who purchased and/or paid for some or all of the purchase price for Restasis and/or its AB-rated generic equivalents in the United States, in any form, for consumption by themselves, their families, or their members, employees, insureds, participants, or beneficiaries (the "Class" or the "End Payor Class"), other than for resale, during the period May 7, 2014 through and until the anticompetitive effects of Defendant's unlawful conduct cease (the "Class Period"). For purposes of the Class definition, persons or entities "purchased" Restasis or its generic equivalent if they paid or reimbursed some or all of the purchase price.

287. The following persons or entities are excluded from the proposed End-Payor Class:

a. Defendant and its officers, directors, management, employees, subsidiaries, or affiliates;

b. All governmental entities, except for governmental funded employee benefit plans;

c. All persons or entities who purchased Restasis or its AB-rated generic equivalent for purposes of resale or directly from Defendant or its affiliates;

d. Fully insured health plans (*i.e.*, Plans that purchased insurance from another third-party payor covering 100% of the Plan's reimbursement obligations to its members);

e. Any "flat co-pay" consumers whose purchases were paid in part by a third party payor and whose co-payment was the same regardless of the retail purchase price;

f. Any "brand loyalist" consumers or third-party payors who purchased Restasis and who did not purchase any AB-rated generic equivalent after such generics became available.

g. Pharmacy benefit managers; and

h. The judges in this case and any members of their immediate families.

288. Members of the End Payor Class are so numerous that joinder is impracticable. Plaintiffs believe that the Class includes hundreds of thousands, if not millions, of consumers, and thousands of third-party payors.120. Plaintiffs' claims are typical of the claims of the members of the End Payor Class. Plaintiffs and all members of the End Payor Class were damaged by the same wrongful conduct of Defendant's, *i.e.*, they paid artificially inflated prices for Restasis and were deprived of the benefits of earlier and more robust competition from cheaper generic versions of Restasis as a result of Defendant's wrongful conduct.

289. Plaintiffs will fairly and adequately protect and represent the interests of the End Payor Class. The interests of the Plaintiffs are coincident with, and not antagonistic to, those of the Class.

290. Plaintiffs are represented by counsel with experience in the prosecution of class action antitrust litigation, and with particular experience with class action antitrust litigation involving pharmaceutical products.

291. Questions of law and fact common to the members of the Class predominate over questions that may affect only individual Class members because Defendant has acted on grounds generally applicable to the entire End Payor Class, thereby making overcharge damages with respect to the Class as a whole appropriate.

292. Questions of law and fact common to the End Payor Class include, but not limited to:

a. Whether Allergan willfully obtained or maintained monopoly power over

b. Whether Allergan obtained the second wave patents by fraud;

c. Whether Allergan unlawfully excluded competitors from the market for Restasis and its AB-rated generic equivalents;

d. Whether Allergan unlawfully delayed or prevented generic manufacturers of cyclosporine ophthalmic emulsion from entering the market in the United States;

e. Whether Allergan possessed monopoly power over Restasis;

f. Whether Allergan's agreement with the Tribe violated Section 1 of the Sherman Act;

g. Whether there was any legitimate business justification for the anticompetitive contract between Allergan and the Tribe, and whether the anticompetitive effects of that contract outweigh any reasonable procompetitive benefits or justifications;

h. Whether Allergan and the Tribe conspired to monopolize the Restasis market;

i. Whether the law requires definition of a relevant market when direct proof of monopoly power is available and, if so, the definition of the relevant market;

j. Whether the activities of Defendant as alleged herein have substantially affected interstate commerce;

k. Whether, and to what extent, Defendant's conduct caused antitrust injury

(*i.e.*, overcharges) to Plaintiffs and the members of the Class; and

l. The quantum of aggregate overcharge damages to the Class.

293. Class action treatment is a superior method for the fair and efficient adjudication of the controversy. Such treatment will permit a large number of similarly situated persons to prosecute their common claims in a single forum simultaneously, efficiently, and without the unnecessary duplication of evidence, effort, or expense that numerous individual actions would engender. The benefits of proceeding through the class mechanism, including providing injured persons or entities a method for obtaining redress on claims that could not practicably be pursued individually, substantially outweighs potential difficulties in management of this class action.

294. Plaintiffs know of no special difficulty to be encountered in the maintenance of this action that would preclude its maintenance as a class action.

VII. MARKET POWER AND DEFINITION

295. The relevant geographic market is the United States and its territories and possessions.

296. At all relevant times, Allergan's share of the relevant cyclosporine ophthalmic emulsion, 0.05% market was and remains 100%.

297. At all relevant times, Allergan had monopoly power in the market for cyclosporine ophthalmic emulsion, 0.05% products. It had the power to maintain the price of Restasis at supra-competitive levels without losing substantial sales to other products prescribed and/or used for the same purposes as Restasis, with the exception of generic cyclosporine ophthalmic emulsion, 0.05% products. This market power may be shown directly, and therefore no relevant market needs to be defined.

298. Allergan has admitted that it has 100% of the applicable market. In October of 2013, Allergan's vice president of marketing swore under oath, in a filing with the PTO, that "[a]s there is no other FDA-approved therapeutic treatment for dry eye available on the US market, Restasis own 100% of the market share." Allergan's patent counsel repeated that statement in a filing that included the declaration.

299. Allergan has enjoyed monopoly power conferred by the Ding I patent since 1995 to May of 2014. It procured the second wave patents to further extend that monopoly.

300. Since 2003, when it launched Restasis pursuant to FDA approval, Allergan has reaped significant commercial benefits. When it received FDA approval in December 2002, Allergan represented Restasis as "the first and only therapy for patients with keratoconjunctivitis sicca (chronic dry eye disease-CDED) whose tear production is presumed to be suppressed due to ocular inflammation." In its numerous filings with the FDA, Allergan has similarly represented Restasis' uniqueness: "RESTASIS is a pathbreaking product that was developed to treat the widespread and sometimes debilitating problem of dry eye disease. Before RESTASIS, dry eye disease was a largely unmet medical need. After years of FDA-required clinical trials, Allergan was able to produce a precisely formulated drug that has significant efficacy in treating dry eye disease."[109]

301. Manufacturers attempt to differentiate brand name drugs like Restasis based on features and benefits (including safety and efficacy), and not based on price. Doctors and patients are generally price-insensitive when prescribing and taking prescription drugs like Restasis. This is due in part to the presence of insurance that bears much of the cost of prescriptions and other institutional features of the pharmaceutical marketplace. Different patients may respond

[109] Allergan, Inc., Citizen Petition, Feb. 28, 2014, at 13.

differently to different drugs and even drugs within its same therapeutic class do not constrain the price of Restasis.

302. Other products are not practical substitutes for cyclosporine. Artificial tears offer only ephemeral relief and do nothing to address the underlying causes of dry eye. Corticosteroids can address the inflammation associated with dry eye, but have unwanted side effects, as do devices like "punctal plugs," which block the tear ducts and help the eye retain naturally produced tears for longer. Patients treated with cyclosporine would not switch to these products in response to a small but significant non-transitory increase in the price of cyclosporine in sufficient numbers to make such a price increase by a hypothetical monopolist unprofitable. Shire US, Inc.'s introduction last year of its rival DED product, Xiidra, has not resulted in lower Restasis prices, thus confirming Allergan's continued market power over the relevant cyclosporine market.

303. Allergan's ability to double the price of Restasis over the past decade without loss of significant sales further demonstrates lack of substitutability between Restasis and other drug products.[110] Restasis does not exhibit significant, positive cross-elasticity of demand with respect to price with any other DED medication. Other various DED treatments may exist, but none exhibit cross price elasticity with and therefore do not constrain the price of Restasis. The existence of these non-cyclosporine products that may be used to treat similar indications as Restasis did not constrain Allergan's ability to raise or maintain Restasis prices without losing substantial sales, and therefore those other drug products are not in the same relevant antitrust market as Restasis. Therapeutic alternatives, to the extent existent, are not the same as economic

[110] *See* David Crow, *Allergan Deal with Mohawk Tribe Casts Patent Shadow*, Fin. Times, Sept. 27, 2017 ("The average wholesale price of a 30-dose pack of Restasis has more than doubled from $117 in 2008 to almost $280 today").

alternatives.

304. Functional similarities between Restasis and other DED medications, other than generic Restasis equivalents, are insufficient to permit inclusion of those other molecules in the relevant market with Restasis. To be an economic substitute for antitrust purposes, a functionally similar product must also exert sufficient pressure on the prices and sales of another product, so that the price of that product cannot be maintained above levels that would otherwise be maintained in a competitive market. No other DED medication (except for generic versions of Restasis) will take way sufficient sales of Restasis to prevent Allergan from raising or maintaining the price of Restasis above levels that would otherwise prevail in a competitive market.

305. Restasis is also not reasonably interchangeable with any products other than generic versions of Restasis because Restasis has significantly differentiating attributes making it a unique drug product. The FDA does not consider Restasis interchangeable with any other medication. Nor does Allergan. For example, Restasis is a topical ophthalmic formulation, and as Allergan has explained, "[u]nlike other drug delivery routes, a topical ophthalmic formulation usually delivers drug to the ocular tissues in relatively short timeframe of a few minutes."[111]

306. Allergan needed to control only Restasis and its generic equivalents, and no other products, to maintain the price of Restasis profitably at supra-competitive prices while preserving all or virtually all of its sales. Only the market entry of a competing, AB-rated generic version of Restasis would render Allergan unable to maintain its monopoly prices of Restasis without losing substantial sales.

[111] Allergan, Inc., Comment re Docket No. FDA 2007 D 0369: June 2013 Draft Bioequivalence Guidance for Cyclosporine Ophthalmic Emulsion, 0.05%, Aug. 17, 2013, at 13.

307. Allergan also sold Restasis at prices well in excess of marginal costs, and substantially in excess of the competitive price, and enjoyed high profit margins.

308. Allergan has exercised its power to exclude and restrict competition to Restasis and its generic equivalents.

309. Allergan, at all relevant times, enjoyed high barriers to entry with respect to competition in the relevant product market of cyclosporine ophthalmic emulsion, 0.05% due, in large part, to legally and illegally created patent protections, legally and illegally created regulatory bars to FDA approval of generic competitors, and high costs of entry and expansion.

310. To the extent Plaintiffs are legally required to prove monopoly power through circumstantial evidence by first defining a relevant product market, Plaintiffs allege that the relevant market is all cyclosporine ophthalmic emulsion, 0.05% products (*i.e.*, Restasis and its generic equivalents). During the period relevant to this case, Allergan has been able to profitably maintain the price of cyclosporine ophthalmic emulsion, 0.05% products well above competitive levels.

VIII. MARKET EFFECTS AND CLASS DAMAGES

311. But for the anticompetitive conduct alleged above, multiple generic manufacturers would have entered the market with their generic cyclosporine ophthalmic emulsion, 0.05% products starting as early as May 17, 2014, when the exclusivity associated with Ding I expired.

312. Instead, Allergan willfully and unlawfully maintained its monopoly power in the market for cyclosporine ophthalmic emulsion, 0.05% through a scheme to exclude competition. The scheme forestalled generic competition and carried out its anticompetitive effect of maintaining supra-competitive prices for Restasis. Allergan implemented its scheme by fraudulently obtaining the second wave patents, wrongfully listing these knowingly invalid patents in the Orange Book, wrongfully enforcing those patents against the generic

manufacturers, submitting baseless citizen petitions to the FDA, otherwise abusing the Hatch-Waxman framework, and entering into an anti-competitive agreement with Mohawk to insulate the second wave patents from invalidation in PTO board *inter partes* proceedings. These acts, individually and in combination, were anticompetitive.

313. If Allergan had not defrauded the PTO, (1) the second wave patents would never have been issued, (2) Allergan could never have used those second wave patents as a vehicle to bring suits, (3) in those suits, that no reasonable pharmaceutical manufacturer in Allergan's position would realistically expect to prevail on the merits.

314. Allergan's anticompetitive conduct had the purpose and effect of restraining competition unreasonably and injuring competition by protecting Restasis from generic competition. Allergan's actions allowed it to maintain a monopoly and exclude competition in the market for cyclosporine ophthalmic emulsion. 0.05%, *i.e.*, Restasis and its generic equivalents, effectively preserving the market solely for the benefit of Allergan's monopoly profits.

315. Allergan's exclusionary conduct has delayed, prevented, and impeded the efficient sale of and competition from generic cyclosporine ophthalmic emulsion, 0.05% in the United States, and unlawfully enabled Allergan to sell Restasis without generic competition (at artificially inflated prices).

316. Allergan's anticompetitive conduct, which delayed the introduction into the U.S. marketplace of any generic version of Restasis, caused Plaintiffs and members of the Class to pay more than they would have paid for cyclosporine ophthalmic emulsion, 0.05%.

IX. ANTITRUST IMPACT

317. During the relevant period, Plaintiffs and members of the Class purchased substantial amounts of Restasis directly from Allergan. As a result of Allergan's unlawful

anticompetitive conduct, Plaintiffs and members of the Class were compelled to pay, and did pay, artificially inflated prices for their cyclosporine ophthalmic emulsion, 0.05% requirements. Those prices were substantially greater than the prices that Plaintiffs and members of the Class would have paid absent the illegal conduct alleged herein, because: (1) the price of brand-name Restasis was artificially inflated by Allergan's illegal conduct, and (2) class members were deprived of the opportunity to purchase lower-priced generic versions of Restasis sooner.

318. As a consequence, Plaintiffs and members of the Class have sustained substantial losses and damage to their business and property in the form of overcharges. The full amount and forms and components of such damages will be calculated after discovery and upon proof at trial.

X. CLAIMS FOR RELIEF

COUNT I
Violation of Section 2 of the Sherman Act, 15 U.S.C. § 2:
Monopolization through Walker Process Fraud

319. Plaintiffs repeat and incorporate by reference all preceding paragraphs and allegations.

320. As described above, from 1995 until the present (and with continuing effects hereafter), Allergan possessed and continues to unlawfully possess monopoly power in the market for cyclosporine ophthalmic emulsion, 0.05%. During the relevant time period, no other manufacturer sold a competing version of any cyclosporine ophthalmic emulsion, 0.05% product in the United States.

321. Allergan has willfully and unlawfully maintained its monopoly power in the Restasis market from May 17, 2014 through at least the present day by wrongfully acquiring by fraud, and then enforcing, the second wave patents to keep generic equivalents from the market—not as a result of providing a superior product, business acumen, or historical accident.

322. Allergan knowingly and intentionally asserted the invalid second wave patents in order to maintain its monopoly power. This was intended to, and in fact had the effect of, blocking and delaying entry of AB-rated generic versions of Restasis.

323. Allergan, by and through its patent attorneys and scientists who submitted declarations in support of patentability (including Laura L. Wine, Dr. Rhett M. Schiffman, and Dr. Mayasa Attar), made misrepresentations of fact to the Patent and Trademark Office. These included:

- Statements by Allergan's patent counsel that Dr. Schiffman's declaration showed "surprisingly, the claimed formulation demonstrated a 8-fold increase in relative efficacy for the Schirmer Teat Test score in the first study of Allergan's Phase 3 trials compares to the relative efficacy for the . . . formulation discussed in Example 1E of Ding, tested in Phase 2 trials . . . . This was clearly a very surprising and unexpected result."

- Statements by Allergan's patent counsel that Dr. Schiffman's declaration showed "the claimed formulations also demonstrated a 4-fold improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a 4-fold increase in relative efficacy for decrease in corneal staining scores in both of the Phase 3 studies compared to the . . . formulation tested in Phase 2 and disclosed in Ding. This was clearly a very surprising and unexpected result."

- Figures 1-4 in Dr. Schiffman's declaration reported figured from the Sall paper but omitted all error bars and p-values. In truth, as the Court later found, none of the pair-wise comparisons between the two cyclosporine formulations for corneal staining and Schirmer scores in the Phase 2 study or the pooled Phase 3 studies demonstrated statistical significance at any time point, and many of the p-values for the pair-wise comparisons were very high.[112] The actual statistical analyses showed that any observed difference in raw numbers between the cyclosporine formulations was likely the result of random chance.

- Dr. Schiffman did not disclose to the PTO that he was comparing different Schirmer tear test scores – one without anesthesia in Phase 2 and one with anesthesia in Phase 3 –to purportedly show a difference in efficacy. As the Court later found, only the Schirmer tear test results with anesthesia in Phase 3 significantly favored the 0.05% cyclosporine formulation. "It was therefore only by comparing the results of two different types of tests that Dr. Schiffman was able to produce a significantly distorted picture suggesting that the [Phase 3

[112] *Allergan* at 76.

formulation' was much more effective than the [Phase 2 formulation]."[113] This was both statistically and clinically improper.

- Dr. Schiffman did not disclose to the PTO that the method he chose to calculate the differences in efficacy "exaggerated the difference in the raw values between the two."[114]

- The calculations in Dr. Schiffman's table are misleading:

  a. Dr. Schiffman used ratios of the degree of improvement, which tends to overstate the difference between the results;

  b. Dr. Schiffman ignored the fact that the Phase 2 study was quite small, and that the difference in the raw numbers between formulations were not statistically significant; and

  c. Dr. Schiffman only included data from favorable comparisons between the two formulations – he omitted categories where the Ding I formulation did better than the second wave formulation.[115]

- Dr. Schiffman did not tell the PTO that the data provided was taken from the Sall paper published more than a dozen years earlier (and three years before the priority date for the Restasis patents). Even if the results presented were surprising (they were not), they were publicly known before the date of invention and cannot be the basis for a claim that it was "unexpected" as of the Restasis patent's priority date.[116]

324. These representations were material. The examiner had repeatedly rejected the applications as obvious before Allergan's misleading statements and omissions. The examiner had also earlier rebuffed Allergan's purported secondary considerations of non-obviousness (including commercial success and unmet need). The PTO board's later decision, as well as the *Allergan* court's later decision, support the materiality of these misrepresentations and omissions.

[113] *Id.* at 76.

[114] *Id.* at 78.

[115] *Id.*

[116] *Id.*

325. Allergan made these statements with intent to deceive the PTO. The misleading statements were made intentionally, not accidentally. Allergan was motivated to obtain a longer period of patent protection, given the large sales of Restasis and the importance of the product to the company. The misleading statements were only made after the examiner rejected the application (not with the initial filing) and were made to overcome a rejection and support patentability. There is no innocent explanation for presenting the information as it was presented in the misleading declaration and accompanying submissions; the only reasonable inference is that Allergan intended to deceive the PTO.

326. The PTO reasonably relied on Allergan's false and misleading statements in issuing the second wave patents. The examiner stated that the Schiffman declaration was deemed sufficient to overcome his earlier rejection based on Ding I because the "Examiner is persuaded that, unexpectedly, the claimed formulation . . . demonstrated an 8-fold increase in relative efficacy for the Schirmer Tear Test score in the first study of Phase 3 trials compared to relative efficacy for the formulation disclosed in Ding I." The Examiner also explained that the declarations "illustrate that the claimed formulations . . . also demonstrate a 4-fold improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a 4-fold increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compare to the . . . formulation tested in Phase 2 and disclosed in Ding . . . ."

327. But for Allergan's misrepresentations and omissions, the second wave patents would not have issued. Had they not issued, there was no patent-based impediment to generic versions of Restasis entering the market from May 17, 2014 onwards.

328. Allergan listed the second wave patents in the Orange Book and later asserted them against all would-be generic competitors.

329. But for Allergan's asserting the fraudulently obtained patent, generic versions of Restasis would have been available as early as May 17, 2014, and in any case within the Class Period.

330. There is no valid procompetitive business justification for Allergan's anticompetitive conduct, and to the extent Allergan offers one, it is pretextual and not cognizable, and any procompetitive benefits of Allergan's conduct do not outweigh its anticompetitive harms.

COUNT II
Violation of Section 2 of the Sherman Act, 15 U.S.C. § 2:
Monopolization through an overarching anticompetitive scheme

331. Plaintiffs repeat and incorporate by reference all preceding paragraphs and allegations.

332. As described above, from 1995 until the present (and with continuing effects hereafter), Allergan possessed and continues to unlawfully possess monopoly power in the market for cyclosporine ophthalmic emulsion, 0.05%. During the relevant time period, no other manufacturer sold a competing version of any cyclosporine ophthalmic emulsion. 0.05% product in the United States.

333. Allergan has willfully and unlawfully maintained its monopoly power in the market for cyclosporine ophthalmic emulsion, 0.05% from May 17, 2014 through at least the present day by engaging in an anticompetitive scheme to keep generic equivalents from the market – not as a result of providing a superior product, business acumen, or historical accident.

334. Allergan knowingly and intentionally engaged in an anticompetitive scheme to maintain its monopoly power, the components of which either standing alone or in combination

(in whole or part) were designed to and in fact have blocked and delayed entry of generic versions of Restasis. This scheme included:

- Prosecuting serial baseless patent applications and ultimately obtaining the second wave patents by fraud through misleading the PTO and failing to exercise the duty of disclosure, candor, and good faith;
- Unlawfully listing the second wave patents in the Orange Book;
- Wrongfully enforcing the second wave patents in multiple lawsuits;
- Submitting serial baseless citizen petitions; and
- Abusing the Patent Trial and Appeal Board's *inter partes* review process through an anticompetitive transfer of the second wave patents to the Saint Regis Mohawk Tribe.

335. By means of this scheme, Allergan intentionally and wrongfully maintained monopoly power with respect to Restasis in violation of Section 2 of the Sherman Act. As a result of this unlawful maintenance of monopoly power, Plaintiffs and members of the Class paid artificially inflated prices for their cyclosporine ophthalmic emulsion, 0.05% product requirements.

336. Plaintiffs and members of the Class have been injured in their business or property by Allergan's antitrust violations. Their injury consists of having paid higher prices for their cyclosporine ophthalmic emulsion, 0.05% product requirements than they would have paid in the absence of those violations. Such injury, called "overcharges," is of the type antitrust laws were designed to prevent, flows from that which makes Allergan's conduct unlawful, and Plaintiffs and the Class are the proper entities to bring a case concerning this conduct.

337. Allergan knowingly and intentionally committed *Walker Process* fraud to induce the PTO to grant the second wave patents. Allergan – after repeated denials of prior substantially similar serial applications over more than a 10-year period – submitted false sworn declarations in 2013, that Allergan characterized, by commission and omission, as presenting new data that

showed surprising results not anticipated by prior art (*i.e.*, Ding I), when in fact the data presented was neither new or surprising. Had Allergan made clear to the PTO examiner that the 2013 declarations statements and data were lifted from prior art known to Allergan for over thirteen years (and which had been published three years before the September 2003 priority date), the PTO examiner would have rejected all of the 2013 applications for the same reasons it had repeatedly denied every prior application: that the claims presented were all obvious in light of the prior art. Allergan's misstatements were material, fraudulent, and made knowingly and with the intent to deceive, and in fact induced the PTO to issue the second wave patents.

338. Allergan knew when it listed the second wave patents in the Orange Book that these patents were fraudulently procured and/or were otherwise invalid as obvious in light of prior art, namely Ding I and the related patents, and that therefore the second wave patents should not have been listed in the Orange Book. Allergan knew that listing the second wave patents in the Orange Book would force ANDA applicants to file paragraph IV certifications that would thereby provide Allergan the opportunity to file patent infringement suits against those ANDA applicants that, regardless of the baselessness of such suit, could trigger an automatic stay of any FDA final approval of any new paragraph IV-certified ANDA applicant's generic Restasis product for a period of up to 30 months.

339. Allergan knowingly and intentionally engaged in multiple sham litigations against manufacturers of AB-rated generic equivalents of Restasis that no reasonable pharmaceutical company in Allergan's position would realistically expect to win. Allergan intentionally and deceptively alleged the generic manufacturers' products infringed its second wave patents, knowing when those suits were filed that such patents were wrongfully obtained though fraud on the PTO and were otherwise invalid as obvious in light of the prior art, namely Ding I and the

related patents. Allergan also knew, at the time those multiple sham suits were filed, that it had no realistic likelihood of success, i.e., that there was no realistic likelihood that a court would enforce the fraudulently-obtained and otherwise invalid second wave patents against a generic company. Allergan knew, therefore, that no reasonable pharmaceutical manufacturer would have believed it had a reasonable chance of succeeding on the merits of these infringement lawsuits. Allergan filed this sham lawsuit for the purposes of using a governmental process as an anticompetitive weapon to keep generics off the market and wrongfully maintain its monopoly power over Restasis, regardless of any actual merit to its infringement claims.

340. Allergan knowingly and intentionally submitted multiple and serial citizen and other petitions to the FDA when no reasonable pharmaceutical manufacturer in Allergan's position would expect the FDA to grant the requested relief. The purpose and intent of these petitions was delay the FDA's approval of any of the pending generic ANDA applications, regardless of any objective merit to any part or parts of any petition.

341. Allergan knowingly and intentionally transferred the second wave patents to Mohawk – a sovereign tribe that does not manufacture or distribute pharmaceutical products of any kind and is better known for its operation of casinos on tribal lands located in New York – in an attempt to evade invalidation of those patents and cessation of its Restasis monopoly, which illustrates the extraordinary measures Allergan was willing to take in its stop-at-nothing desperation to delay competition.

342. Allergan's anticompetitive conduct is not entitled to any qualified *Noerr-Pennington* immunity, nor is it protected by the state action doctrine.

343. There is no valid procompetitive business justification for Allergan's anticompetitive conduct, and to the extent Allergan offers one, it is pretextual and not

cognizable, and any procompetitive benefits of Allergan's conduct do not outweigh its anticompetitive harms.

COUNT III
Violation of Section 1 of the Sherman Act, 15 U.S.C. §1:
Contract in restraint of trade

344. Plaintiffs repeat and incorporate by reference all preceding paragraphs and allegations.

345. Allergan entered into a contract, with Mohawk in unreasonable restraint of trade in violation of Section 1 of the Sherman Act, 15 U.S.C. § 1.

346. Allergan's contract in restraint of trade and its other anticompetitive acts were intentionally directed at the United States Restasis market, and had a substantial and foreseeable effect on interstate commerce by interfering with potential generic competition for Restasis and raising and maintaining Restasis prices at supra-competitive levels throughout the United States.

347. As a result of the contract in restraint of trade, Allergan and Mohawk have effectively excluded competition from the Restasis market, allowing Allergan to unlawfully maintain its monopoly in the Restasis market, and both Allergan and Mohawk have profited from their illegal contract by maintaining prices at artificially high levels.

348. There is no legitimate business justification for the anti-competitive actions of Allergan and Mohawk and the conduct through which Allergan maintained its monopoly in the market, including the contract between Allergan and Mohawk. The anticompetitive effects of Allergan's and Mohawk's contract far outweigh any conceivable pro-competitive benefit or justification.

349. As a direct and proximate result of Allergan's and Mohawk's unlawful actions, Plaintiffs and members of the Class were injured in their business or property.

350. As a direct and proximate result of Allergan's and Mohawk's unlawful actions, Plaintiffs and the other members of the Class have been forced to pay artificially high, supra-competitive prices for Restasis and were harmed thereby.

351. Plaintiffs and members of the Class are entitled to treble damages to remedy the injuries they have suffered from Allergan's violations of Sherman Act § 1, 15 U.S.C. § 1.

COUNT IV
Violation of Section 2 of the Sherman Act, 15 U.S.C. §2:
Conspiracy to monopolize

352. Plaintiffs repeat and incorporate by reference all preceding paragraphs and allegations.

353. Allergan and Mohawk have conspired to allow Allergan to willfully maintain and unlawfully exercise monopoly power in the Restasis market through the anti-competitive contract with the specific intent to monopolize the Restasis market, and preventing competition in the market.

354. As a result of the conspiracy, Allergan and Mohawk have effectively excluded competition from the Restasis market, unlawfully maintained Allergan's monopoly in the Restasis market, and profited from their anti-competitive conduct by maintaining prices at artificially high levels.

355. As a result of the contract in restraint of trade, Allergan and Mohawk have effectively excluded competition from the Restasis market, allowing Allergan to unlawfully maintain its monopoly in the Restasis market, including the contract between Allergan and Mohawk. The anti-competitive effects of Allergan's and Mohawk's contract far outweigh any conceivable pro-competitive benefit or justification.

356. There is no legitimate business justification for the anti-competitive actions of Allergan and Mohawk and the conduct through which Allergan maintained its monopoly in the market. The anti-competitive effects of Allergan's and Mohawk's agreement far outweigh any conceivable pro-competitive benefit or justification.

357. As a direct and proximate result of Allergan's and Mohawk's unlawful actions, Plaintiffs and members of the Class have been and continue to be injured in their business or property.

358. As a direct and proximate result of Allergan's and Mohawk's unlawful actions, Plaintiffs and the other members of the Class have been forced to pay artificially high, supra-competitive prices for Restasis and were harmed thereby.

359. Plaintiffs and members of the Class are entitled to treble damages to remedy the injuries they have suffered from Allergan's violations of Sherman Act § 2, 15 U.S.C. § 2.

XI. DEMAND FOR RELIEF

WHEREFORE, Plaintiffs, on behalf of themselves and the proposed class, respectfully demand that the Court:

i. Determine that this action may be maintained as a class action pursuant to Fed. R. Civ. P. Rule 23(a) and (b)(3), and direct that reasonable notice of this action, as provided by Rule 23(c)(2), be given to the Class, and declare Plaintiffs as named representatives of the Class;

ii. Conduct expedited discovery proceedings leading to a prompt trial on the merits before a jury on all claims and defenses;

iii. Enter judgment against Allergan and in favor of Plaintiffs and the Class;

iv. Award the Class damages (*i.e.*, three times overcharges) in an amount to be determined at trial, plus interest in accordance with law;

v. Award Plaintiffs and the Class their costs of suit, including reasonable attorneys' fees as provided by law; and

vi. Award such further and additional relief as is necessary to correct for the

anticompetitive market effects caused by Allergan's unlawful conduct, as the Court may deem just and proper under the circumstances.

XII. JURY DEMAND

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Plaintiffs, on behalf of themselves and the proposed class, demands a trial by jury on all issues so triable.

Dated February 26, 2018

Respectfully submitted:

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